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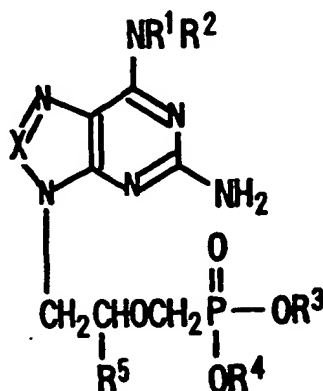
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(54) PHOSPHONATE NUCLEOTIDE DERIVATIVES

(57) A compound represented by the following general formula (I) which has an antiviral activity:



(I)

wherein R¹ represents hydrogen atom, C₁-C₆ alkyl group, or C₇-C₁₀ aralkyl group; R² represents C₁-C₆ alkyl group, C₇-C₁₀ aralkyl group, or phenyl group; R³ and R⁴ independently represent hydrogen atom, C₁-C₆ alkyl group, acyloxymethyl group, acylthioethyl group, or ethyl group substituted with at least one halogen atom; R⁵ represents hydrogen atom, C₁-C₄ alkyl group, C₁-C₄ hydroxyalkyl group, C₁-C₄ alkyl group substituted with at least one halogen atom; and X represents carbon atom or nitrogen atom.

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Description

Technical Field

5 The present invention relates to novel phosphonate nucleotide derivatives. More specifically, it relates to novel phosphonate nucleotide derivatives which have antiviral activity and are useful as active ingredients of medicaments

Background Art

10 Viral infectious diseases are recognized as a major medical problem, and to achieve therapeutic treatment of these diseases, it has been attempted to develop medicaments having antiviral activity and not exhibiting growth inhibitory activity on healthy cellular systems. For example, a class of phosphonate nucleotides has been intensively studied recently as compounds having selective toxicity against viruses. More specifically, it has been reported that 9-(2-phosphorylmethoxy)ethyladenine (PMEA), 9-(2-phosphorylmethoxy)ethyl-2,6-diaminopurine (PMDAP) and the like are
 15 effective against herpes simplex viruses type-1 and type-2 (HSV-1 and HSV-2), human immunodeficiency virus (HIV), and human hepatitis B virus (HBV) (Yokota et al., Antimicrob. Agents Chemother., 35, 394 (1991); and Votruba et al. Mol. Pharmacol., 32, 524 (1987)).

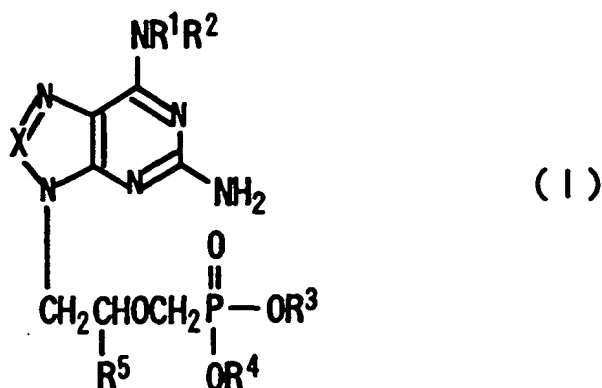
However, these known phosphonate nucleotides may possibly have toxicity to a living body, including myeloid cell growth inhibition as a typical example, and mutagenicity, and their problems have been pointed out from a viewpoint of
 20 safety (Antiviral Research, 16, 77 (1991)). In addition, these compounds have insufficient oral absorbability (DeClercq et al., Antimicrob. Agents Chemother., 33, 185 (1989)), and accordingly, parenteral administration such as intravenous injection or intramuscular injection is unavoidably applied in order to obtain an essential blood concentration for exhibiting efficacy. Therapeutic treatment by parenteral administration cannot be applied to patients other than inpatients, and such method is undesired for treatment of diseases such as AIDS or hepatitis B virus infectious disease which
 25 require long-term therapy.

On the other hand, the inventors of the present invention found that specific ester derivatives of phosphonate nucleotides have antiviral activity and high oral absorbability (European Patent Publication No. 632,048). However, the derivatives have not yet been clinically developed.

30 Disclosure of the Invention

The inventors of the present invention conducted intensive researches to solve the foregoing problems, and a result, they found that a specific class of phosphonate nucleotides having novel chemical structures have higher antiviral activity compared to compounds already reported, and that they are safer to a living body and have high oral absorbability. The present invention was achieved on the basis of these findings.

The present invention thus provides phosphonate nucleotide derivatives represented by the following general formula (I) and salts thereof, and hydrates and solvates thereof:



In the above formula, R¹ represents hydrogen atom, a C₁-C₆ alkyl group, or a C₇-C₁₀ aralkyl group; R² represents a C₁-C₆ alkyl group, a C₇-C₁₀ aralkyl group, or phenyl group, R³ and R⁴ each independently represent hydrogen atom,

a C₁-C₆ alkyl group, an acyloxymethyl group, an acythioethyl group, or an ethyl group substituted with one or more halogen atoms; R⁵ represents hydrogen atom, a C₁-C₄ alkyl group, a C₁-C₄ hydroxyalkyl group, or a C₁-C₄ alkyl group substituted with one or more halogen atoms; and X represents carbon atom or nitrogen atom.

According to further embodiments of the present invention, there are provided medicaments comprising the above substances; pharmaceutical compositions and antiviral agents comprising the above substances as an active ingredient. In addition, there are also provided uses of the above substances for the manufacture of pharmaceutical compositions having antiviral activity, and methods for treatment of viral infectious diseases comprising the step of administering a therapeutically effective amount of the above substance to a patient.

10 Best Mode for Carrying Out the Invention

In the phosphonate nucleotide derivatives of the above general formula (I), examples of the C₁-C₆ alkyl group represented by R¹, R², R³, and R⁴ include, for example, methyl group, ethyl group, n-propyl group, isopropyl group, n-butyl group, isobutyl group, sec-butyl group, tert-butyl group, n-pentyl group, n-hexyl group or the like.

15 Examples of the C₇-C₁₀ aralkyl group represented by R¹ and R² include, for example, benzyl group, phenethyl group, phenylpropyl group, phenylbutyl group or the like.

In particular, hydrogen atom and a C₁-C₄ alkyl group are preferred as R¹, and a C₁-C₄ alkyl group, benzyl group, and phenyl group are preferred as R². As R², a C₁-C₄ alkyl group and phenyl group are particularly preferred. The C₁-C₄ alkyl group represented by R⁵ may be, for example, methyl group, ethyl group, n-propyl group, isopropyl group, n-butyl group, isobutyl group, sec-butyl group, tert-butyl group or the like.

The acyloxymethyl group represented by R³ and R⁴ may be, for example, acetyloxymethyl group, propionyloxymethyl group, butyryloxymethyl group, isobutyryloxymethyl group, valeryloxymethyl group, isovaleryloxymethyl group, pivaloyloxymethyl group or the like.

25 The acythioethyl group represented by R³ and R⁴ may be, for example, acetylthioethyl group, propionylthioethyl group, butyrylthioethyl group, isobutyrylthioethyl group, valerylthioethyl group, isovalerylthioethyl group, pivaloylthioethyl group or the like.

In the ethyl group substituted with one or more halogen atoms represented by R³ and R⁴, the halogen atom includes fluorine atom, chlorine atom, bromine atom, and iodine atom. Examples of the ethyl group substituted with one or more halogen atoms include 1-fluoroethyl group, 2-fluoroethyl group, 1-chloroethyl group, 2-chloroethyl group, 2-bromoethyl group, 2,2-difluoroethyl group, 2,2-dichloroethyl group, 2,2-dibromoethyl group, 2,2,2-trifluoroethyl group, 2,2,2-trichloroethyl group, 2,2,2-tribromoethyl group and the like. In particular, ethyl groups substituted at the 2-position are preferred, and fluorine atom is preferred as the halogen atom.

As R³ and R⁴, a C₁-C₆ alkyl group or an ethyl group substituted with one or more halogen atoms are preferred, and 2,2,2-trifluoroethyl group is particularly preferred.

35 Examples of the C₁-C₄ hydroxyalkyl group represented by R⁵ include hydroxymethyl group, 1-hydroxyethyl group, 2-hydroxyethyl group, 1-hydroxypropyl group, 2-hydroxypropyl group, 3-hydroxypropyl group, 1-hydroxybutyl group, 2-hydroxybutyl group, 3-hydroxybutyl group, 4-hydroxybutyl group and the like.

In the C₁-C₄ alkyl group substituted with one or more halogen atoms represented by R⁵, examples of the halogen atom include fluorine atom and chlorine atoms or the like, and examples of the C₁-C₄ alkyl group include methyl group, ethyl group, n-propyl group, isopropyl group, n-butyl group, isobutyl group, sec-butyl group, tert-butyl group or the like. 40 Examples of the C₁-C₄ alkyl group substituted with one or more halogen atoms include fluoromethyl group, difluoromethyl group, trifluoromethyl group, fluoroethyl group, chloroethyl group, fluoropropyl group, chloropropyl group, fluorobutyl group, chlorobutyl group and the like.

Hydrogen atom or a C₁-C₄ alkyl group is preferred as R⁵.

45 The compounds of the present invention are characterized in that they have higher antiviral activity compared to a compound disclosed in European Patent Publication No. 632,048, which is derived by the replacement of the amino group at the 6-position of purine ring with a substituted amino group, and that they are safer to living bodies and can achieve higher oral absorbability. Among the compounds of the present invention, it has been found that those having phenyl group as R² are characterized to have lower toxicity compared to those having an alkyl group or aralkyl group as R², and those having an alkyl group as R⁵ are characterized to have lower toxicity compared to those having hydrogen atom, hydroxyalkyl group, or an alkyl group substituted with one or more halogen atoms as R⁵.

Examples of particularly preferred compounds among the compounds of the present invention include:

2-amino-9-[2-bis(2,2,2-trifluoroethyl)phosphonylmethoxy]ethyl]-6-(phenylamino)purine;
 2-amino-9-[2-bis(2,2,2-trifluoroethyl)phosphonylmethoxy]ethyl]-6-(N-methylphenylamino)purine;
 2-amino-9-[2-bis(2,2,2-trifluoroethyl)phosphonylmethoxy]propyl]-6-(phenylamino)purine;
 2-amino-9-[2-bis(2,2,2-trifluoroethyl)phosphonylmethoxy]propyl]-6-(N-methylphenylamino)purine; and
 2-amino-9-[2-bis(2,2,2-trifluoroethyl)phosphonylmethoxy]propyl]-6-(dimethylamino)purine.

5 The phosphonate nucleotide derivatives of the present invention represented by the above general formula (I) may form pharmacologically and pharmaceutically acceptable salts. Specific examples of such salts include, when they have an acidic group, a metal salt such as lithium salt, sodium salt, potassium salt, magnesium salt, and calcium salt, an ammonium salt such as ammonium salt, methylammonium salt, dimethylammonium salt, trimethylammonium salt, and dicyclohexylammonium salt and other. When a basic group exists, they can form mineral acid salts such as hydrochloride, hydrobromide, sulfate, nitrate, and phosphate, or organic acid salts such as methanesulfonate, benzenesulfonate, p-toluenesulfonate, acetate, propionate, tartrate, fumarate, maleate, malate, oxalate, succinate, citrate, benzoate, mandelate, cinnamate, and lactate.

10 The phosphonate nucleotide derivatives of the present invention represented by the above general formula (I) and salts thereof may exist in the form of a hydrate or a solvate. Examples of solvents which can form the solvate include methanol, ethanol, isopropanol, acetone, ethyl acetate, methylene chloride and the like. It should be understood that the compounds represented by the general formula (I) as a free form and salts thereof, and their hydrates and solvates fall within the scope of the present invention.

15 Specific examples of the compound of the present invention are shown in Table 1 set out below. In the table, "Me" represents methyl group, "Et" represents ethyl group, "n-Pr" represents n-propyl group, "i-Pr" represents isopropyl group, "n-Bu" represents n-butyl group, "t-Bu" represents tertiary butyl group, and "Ph" represents phenyl group.

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Table 1

	Com- pound No.	R ¹	R ²	R ³	R ⁴	R ⁵	X
5	1	H	Me	CF ₃ CH ₂ -	CF ₃ CH ₂ -	H	C
	2	H	Et	CF ₃ CH ₂ -	CF ₃ CH ₂ -	H	C
10	3	H	n-Pr	CF ₃ CH ₂ -	CF ₃ CH ₂ -	H	C
	4	H	i-Pr	CF ₃ CH ₂ -	CF ₃ CH ₂ -	H	C
	5	H	n-Bu	CF ₃ CH ₂ -	CF ₃ CH ₂ -	H	C
15	6	H	Me	CF ₃ CH ₂ -	CF ₃ CH ₂ -	H	N
	7	H	Et	CF ₃ CH ₂ -	CF ₃ CH ₂ -	H	N
	8	H	n-Pr	CF ₃ CH ₂ -	CF ₃ CH ₂ -	H	N
	9	H	i-Pr	CF ₃ CH ₂ -	CF ₃ CH ₂ -	H	N
20	10	H	n-Bu	CF ₃ CH ₂ -	CF ₃ CH ₂ -	H	N
	11	Me	Me	CF ₃ CH ₂ -	CF ₃ CH ₂ -	H	C
	12	Me	Et	CF ₃ CH ₂ -	CF ₃ CH ₂ -	H	C
25	13	Me	n-Pr	CF ₃ CH ₂ -	CF ₃ CH ₂ -	H	C
	14	Me	i-Pr	CF ₃ CH ₂ -	CF ₃ CH ₂ -	H	C
	15	Me	n-Bu	CF ₃ CH ₂ -	CF ₃ CH ₂ -	H	C
	16	Et	Et	CF ₃ CH ₂ -	CF ₃ CH ₂ -	H	C
30	17	Et	n-Pr	CF ₃ CH ₂ -	CF ₃ CH ₂ -	H	C
	18	Et	i-Pr	CF ₃ CH ₂ -	CF ₃ CH ₂ -	H	C
	19	Et	n-Bu	CF ₃ CH ₂ -	CF ₃ CH ₂ -	H	C
35	20	n-Pr	n-Pr	CF ₃ CH ₂ -	CF ₃ CH ₂ -	H	C
	21	Me	Me	CF ₃ CH ₂ -	CF ₃ CH ₂ -	H	N
	22	Me	Et	CF ₃ CH ₂ -	CF ₃ CH ₂ -	H	N
	23	Me	n-Pr	CF ₃ CH ₂ -	CF ₃ CH ₂ -	H	N
40	24	Me	i-Pr	CF ₃ CH ₂ -	CF ₃ CH ₂ -	H	N
	25	Me	n-Bu	CF ₃ CH ₂ -	CF ₃ CH ₂ -	H	N
	26	Et	Et	CF ₃ CH ₂ -	CF ₃ CH ₂ -	H	N
	27	Et	n-Pr	CF ₃ CH ₂ -	CF ₃ CH ₂ -	H	N
45	28	Et	i-Pr	CF ₃ CH ₂ -	CF ₃ CH ₂ -	H	N
	29	Et	n-Bu	CF ₃ CH ₂ -	CF ₃ CH ₂ -	H	N
	30	n-Pr	n-Pr	CF ₃ CH ₂ -	CF ₃ CH ₂ -	H	N
50	31	H	Me	Me	CF ₃ CH ₂ -	H	C
	32	H	Et	Me	CF ₃ CH ₂ -	H	C
	33	H	n-Pr	Me	CF ₃ CH ₂ -	H	C

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	34	H	i-Pr	Me	CF ₃ CH ₂ -	H	C
	35	H	n-Bu	Me	CF ₃ CH ₂ -	H	C
5	36	H	Me	Me	CF ₃ CH ₂ -	H	N
	37	H	Et	Me	CF ₃ CH ₂ -	H	N
	38	H	n-Pr	Me	CF ₃ CH ₂ -	H	N
	39	H	i-Pr	Me	CF ₃ CH ₂ -	H	N
10	40	H	n-Bu	Me	CF ₃ CH ₂ -	H	N
	41	Me	Me	Me	CF ₃ CH ₂ -	H	C
	42	Me	Et	Me	CF ₃ CH ₂ -	H	C
15	43	Me	n-Pr	Me	CF ₃ CH ₂ -	H	C
	44	Me	i-Pr	Me	CF ₃ CH ₂ -	H	C
	45	Me	n-Bu	Me	CF ₃ CH ₂ -	H	C
	46	Et	Et	Me	CF ₃ CH ₂ -	H	C
20	47	Et	n-Pr	Me	CF ₃ CH ₂ -	H	C
	48	Et	i-Pr	Me	CF ₃ CH ₂ -	H	C
	49	Et	n-Bu	Me	CF ₃ CH ₂ -	H	C
	50	n-Pr	n-Pr	Me	CF ₃ CH ₂ -	H	C
25	51	Me	Me	Me	CF ₃ CH ₂ -	H	N
	52	Me	Et	Me	CF ₃ CH ₂ -	H	N
	53	Me	n-Pr	Me	CF ₃ CH ₂ -	H	N
30	54	Me	i-Pr	Me	CF ₃ CH ₂ -	H	N
	55	Me	n-Bu	Me	CF ₃ CH ₂ -	H	N
	56	Et	Et	Me	CF ₃ CH ₂ -	H	N
	57	Et	n-Pr	Me	CF ₃ CH ₂ -	H	N
35	58	Et	i-Pr	Me	CF ₃ CH ₂ -	H	N
	59	Et	n-Bu	Me	CF ₃ CH ₂ -	H	N
	60	n-Pr	n-Pr	Me	CF ₃ CH ₂ -	H	N
	61	H	Me	CF ₃ CH ₂ -	H	H	C
40	62	H	Et	CF ₃ CH ₂ -	H	H	C
	63	H	n-Pr	CF ₃ CH ₂ -	H	H	C
	64	H	i-Pr	CF ₃ CH ₂ -	H	H	C
45	65	H	n-Bu	CF ₃ CH ₂ -	H	H	C
	66	H	Me	CF ₃ CH ₂ -	H	H	N
	67	H	Et	CF ₃ CH ₂ -	H	H	N
	68	H	n-Pr	CF ₃ CH ₂ -	H	H	N
50	69	H	i-Pr	CF ₃ CH ₂ -	H	H	N
	70	H	n-Bu	CF ₃ CH ₂ -	H	H	N
	71	Me	Me	CF ₃ CH ₂ -	H	H	C
55							

	72	Me	Et	CF ₃ CH ₂ -	H	H	C
	73	Me	n-Pr	CF ₃ CH ₂ -	H	H	C
5	74	Me	i-Pr	CF ₃ CH ₂ -	H	H	C
	75	Me	n-Bu	CF ₃ CH ₂ -	H	H	C
	76	Et	Et	CF ₃ CH ₂ -	H	H	C
	77	Et	n-Pr	CF ₃ CH ₂ -	H	H	C
10	78	Et	i-Pr	CF ₃ CH ₂ -	H	H	C
	79	Et	n-Bu	CF ₃ CH ₂ -	H	H	C
	80	n-Pr	n-Pr	CF ₃ CH ₂ -	H	H	C
15	81	Me	Me	CF ₃ CH ₂ -	H	H	N
	82	Me	Et	CF ₃ CH ₂ -	H	H	N
	83	Me	n-Pr	CF ₃ CH ₂ -	H	H	N
	84	Me	i-Pr	CF ₃ CH ₂ -	H	H	N
20	85	Me	n-Bu	CF ₃ CH ₂ -	H	H	N
	86	Et	Et	CF ₃ CH ₂ -	H	H	N
	87	Et	n-Pr	CF ₃ CH ₂ -	H	H	N
	88	Et	i-Pr	CF ₃ CH ₂ -	H	H	N
25	89	Et	n-Bu	CF ₃ CH ₂ -	H	H	N
	90	n-Pr	n-Pr	CF ₃ CH ₂ -	H	H	N
	91	H	Me	H	H	H	C
	92	H	Et	H	H	H	C
30	93	H	n-Pr	H	H	H	C
	94	H	i-Pr	H	H	H	C
	95	H	n-Bu	H	H	H	C
35	96	H	Me	H	H	H	N
	97	H	Et	H	H	H	N
	98	H	n-Pr	H	H	H	N
	99	H	i-Pr	H	H	H	N
40	100	H	n-Bu	H	H	H	N
	101	Me	Me	H	H	H	C
	102	Me	Et	H	H	H	C
	103	Me	n-Pr	H	H	H	C
45	104	Me	i-Pr	H	H	H	C
	105	Me	n-Bu	H	H	H	C
	106	Et	Et	H	H	H	C
50	107	Et	n-Pr	H	H	H	C
	108	Et	i-Pr	H	H	H	C
	109	Et	n-Bu	H	H	H	C

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	110	n-Pr	n-Pr	H	H	H	C
	111	Me	Me	H	H	H	N
5	112	Me	Et	H	H	H	N
	113	Me	n-Pr	H	H	H	N
	114	Me	i-Pr	H	H	H	N
	115	Me	n-Bu	H	H	H	N
10	116	Et	Et	H	H	H	N
	117	Et	n-Pr	H	H	H	N
	118	Et	i-Pr	H	H	H	N
	119	Et	n-Bu	H	H	H	N
15	120	n-Pr	n-Pr	H	H	H	N
	121	H	-CH ₂ -Ph	CF ₃ CH ₂ -	CF ₃ CH ₂ -	H	C
	122	H	-CH ₂ -Ph	H	CF ₃ CH ₂ -	H	C
20	123	H	-CH ₂ -Ph	Me	CF ₃ CH ₂ -	H	C
	124	H	-CH ₂ -Ph	H	H	H	C
	125	H	-CH ₂ -Ph	CF ₃ CH ₂ -	CF ₃ CH ₂ -	H	N
	126	H	-CH ₂ -Ph	Me	CF ₃ CH ₂ -	H	N
25	127	H	-CH ₂ -Ph	H	CF ₃ CH ₂ -	H	N
	128	H	-CH ₂ -Ph	H	H	H	N
	129	Me	-CH ₂ -Ph	CF ₃ CH ₂ -	CF ₃ CH ₂ -	H	C
30	130	Me	-CH ₂ -Ph	Me	CF ₃ CH ₂ -	H	C
	131	Me	-CH ₂ -Ph	H	CF ₃ CH ₂ -	H	C
	132	Me	-CH ₂ -Ph	H	H	H	C
	133	Me	-CH ₂ -Ph	CF ₃ CH ₂ -	CF ₃ CH ₂ -	H	N
35	134	Me	-CH ₂ -Ph	Me	CF ₃ CH ₂ -	H	N
	135	Me	-CH ₂ -Ph	H	CF ₃ CH ₂ -	H	N
	136	Me	-CH ₂ -Ph	H	H	H	N
	137	H	Me	CF ₃ CH ₂ -	CF ₃ CH ₂ -	-CH ₂ F	C
40	138	H	Et	CF ₃ CH ₂ -	CF ₃ CH ₂ -	-CH ₂ F	C
	139	H	n-Pr	CF ₃ CH ₂ -	CF ₃ CH ₂ -	-CH ₂ F	C
	140	H	i-Pr	CF ₃ CH ₂ -	CF ₃ CH ₂ -	-CH ₂ F	C
	141	H	n-Bu	CF ₃ CH ₂ -	CF ₃ CH ₂ -	-CH ₂ F	C
45	142	H	Me	CF ₃ CH ₂ -	CF ₃ CH ₂ -	-CH ₂ F	N
	143	H	Et	CF ₃ CH ₂ -	CF ₃ CH ₂ -	-CH ₂ F	N
	144	H	n-Pr	CF ₃ CH ₂ -	CF ₃ CH ₂ -	-CH ₂ F	N
50	145	H	i-Pr	CF ₃ CH ₂ -	CF ₃ CH ₂ -	-CH ₂ F	N
	146	H	n-Bu	CF ₃ CH ₂ -	CF ₃ CH ₂ -	-CH ₂ F	N
	147	Me	Me	CF ₃ CH ₂ -	CF ₃ CH ₂ -	-CH ₂ F	C

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	148	Me	Et	CF ₃ CH ₂ -	CF ₃ CH ₂ -	-CH ₂ F	C
	149	Me	n-Pr	CF ₃ CH ₂ -	CF ₃ CH ₂ -	-CH ₂ F	C
5	150	Me	i-Pr	CF ₃ CH ₂ -	CF ₃ CH ₂ -	-CH ₂ F	C
	151	Me	n-Bu	CF ₃ CH ₂ -	CF ₃ CH ₂ -	-CH ₂ F	C
	152	Et	Et	CF ₃ CH ₂ -	CF ₃ CH ₂ -	-CH ₂ F	C
	153	Et	n-Pr	CF ₃ CH ₂ -	CF ₃ CH ₂ -	-CH ₂ F	C
10	154	Et	i-Pr	CF ₃ CH ₂ -	CF ₃ CH ₂ -	-CH ₂ F	C
	155	Et	n-Bu	CF ₃ CH ₂ -	CF ₃ CH ₂ -	-CH ₂ F	C
	156	n-Pr	n-Pr	CF ₃ CH ₂ -	CF ₃ CH ₂ -	-CH ₂ F	C
15	157	Me	Me	CF ₃ CH ₂ -	CF ₃ CH ₂ -	-CH ₂ F	N
	158	Me	Et	CF ₃ CH ₂ -	CF ₃ CH ₂ -	-CH ₂ F	N
	159	Me	n-Pr	CF ₃ CH ₂ -	CF ₃ CH ₂ -	-CH ₂ F	N
	160	Me	i-Pr	CF ₃ CH ₂ -	CF ₃ CH ₂ -	-CH ₂ F	N
20	161	Me	n-Bu	CF ₃ CH ₂ -	CF ₃ CH ₂ -	-CH ₂ F	N
	162	Et	Et	CF ₃ CH ₂ -	CF ₃ CH ₂ -	-CH ₂ F	N
	163	Et	n-Pr	CF ₃ CH ₂ -	CF ₃ CH ₂ -	-CH ₂ F	N
	164	Et	i-Pr	CF ₃ CH ₂ -	CF ₃ CH ₂ -	-CH ₂ F	N
25	165	Et	n-Bu	CF ₃ CH ₂ -	CF ₃ CH ₂ -	-CH ₂ F	N
	166	n-Pr	n-Pr	CF ₃ CH ₂ -	CF ₃ CH ₂ -	-CH ₂ F	N
	167	H	Me	Me	CF ₃ CH ₂ -	-CH ₂ F	C
30	168	H	Et	Me	CF ₃ CH ₂ -	-CH ₂ F	C
	169	H	n-Pr	Me	CF ₃ CH ₂ -	-CH ₂ F	C
	170	H	i-Pr	Me	CF ₃ CH ₂ -	-CH ₂ F	C
	171	H	n-Bu	Me	CF ₃ CH ₂ -	-CH ₂ F	C
35	172	H	Me	Me	CF ₃ CH ₂ -	-CH ₂ F	N
	173	H	Et	Me	CF ₃ CH ₂ -	-CH ₂ F	N
	174	H	n-Pr	Me	CF ₃ CH ₂ -	-CH ₂ F	N
	175	H	i-Pr	Me	CF ₃ CH ₂ -	-CH ₂ F	N
40	176	H	n-Bu	Me	CF ₃ CH ₂ -	-CH ₂ F	N
	177	Me	Me	Me	CF ₃ CH ₂ -	-CH ₂ F	C
	178	Me	Et	Me	CF ₃ CH ₂ -	-CH ₂ F	C
45	179	Me	n-Pr	Me	CF ₃ CH ₂ -	-CH ₂ F	C
	180	Me	i-Pr	Me	CF ₃ CH ₂ -	-CH ₂ F	C
	181	Me	n-Bu	Me	CF ₃ CH ₂ -	-CH ₂ F	C
	182	Et	Et	Me	CF ₃ CH ₂ -	-CH ₂ F	C
50	183	Et	n-Pr	Me	CF ₃ CH ₂ -	-CH ₂ F	C
	184	Et	i-Pr	Me	CF ₃ CH ₂ -	-CH ₂ F	C
	185	Et	n-Bu	Me	CF ₃ CH ₂ -	-CH ₂ F	C

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5	186	n-Pr	n-Pr	Me	CF ₃ CH ₂ -	-CH ₂ F	C
	187	Me	Me	Me	CF ₃ CH ₂ -	-CH ₂ F	N
	188	Me	Et	Me	CF ₃ CH ₂ -	-CH ₂ F	N
	189	Me	n-Pr	Me	CF ₃ CH ₂ -	-CH ₂ F	N
	190	Me	i-Pr	Me	CF ₃ CH ₂ -	-CH ₂ F	N
10	191	Me	n-Bu	Me	CF ₃ CH ₂ -	-CH ₂ F	N
	192	Et	Et	Me	CF ₃ CH ₂ -	-CH ₂ F	N
	193	Et	n-Pr	Me	CF ₃ CH ₂ -	-CH ₂ F	N
	194	Et	i-Pr	Me	CF ₃ CH ₂ -	-CH ₂ F	N
15	195	Et	n-Bu	Me	CF ₃ CH ₂ -	-CH ₂ F	N
	196	n-Pr	n-Pr	Me	CF ₃ CH ₂ -	-CH ₂ F	N
	197	H	Me	CF ₃ CH ₂ -	H	-CH ₂ F	C
20	198	H	Et	CF ₃ CH ₂ -	H	-CH ₂ F	C
	199	H	n-Pr	CF ₃ CH ₂ -	H	-CH ₂ F	C
	200	H	i-Pr	CF ₃ CH ₂ -	H	-CH ₂ F	C
	201	H	n-Bu	CF ₃ CH ₂ -	H	-CH ₂ F	C
	202	H	Me	CF ₃ CH ₂ -	H	-CH ₂ F	N
25	203	H	Et	CF ₃ CH ₂ -	H	-CH ₂ F	N
	204	H	n-Pr	CF ₃ CH ₂ -	H	-CH ₂ F	N
	205	H	i-Pr	CF ₃ CH ₂ -	H	-CH ₂ F	N
	206	H	n-Bu	CF ₃ CH ₂ -	H	-CH ₂ F	N
30	207	Me	Me	CF ₃ CH ₂ -	H	-CH ₂ F	C
	208	Me	Et	CF ₃ CH ₂ -	H	-CH ₂ F	C
	209	Me	n-Pr	CF ₃ CH ₂ -	H	-CH ₂ F	C
35	210	Me	i-Pr	CF ₃ CH ₂ -	H	-CH ₂ F	C
	211	Me	n-Bu	CF ₃ CH ₂ -	H	-CH ₂ F	C
	212	Et	Et	CF ₃ CH ₂ -	H	-CH ₂ F	C
	213	Et	n-Pr	CF ₃ CH ₂ -	H	-CH ₂ F	C
40	214	Et	i-Pr	CF ₃ CH ₂ -	H	-CH ₂ F	C
	215	Et	n-Bu	CF ₃ CH ₂ -	H	-CH ₂ F	C
	216	n-Pr	n-Pr	CF ₃ CH ₂ -	H	-CH ₂ F	C
45	217	Me	Me	CF ₃ CH ₂ -	H	-CH ₂ F	N
	218	Me	Et	CF ₃ CH ₂ -	H	-CH ₂ F	N
	219	Me	n-Pr	CF ₃ CH ₂ -	H	-CH ₂ F	N
	220	Me	i-Pr	CF ₃ CH ₂ -	H	-CH ₂ F	N
50	221	Me	n-Bu	CF ₃ CH ₂ -	H	-CH ₂ F	N
	222	Et	Et	CF ₃ CH ₂ -	H	-CH ₂ F	N
	223	Et	n-Pr	CF ₃ CH ₂ -	H	-CH ₂ F	N

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5	224	Et	i-Pr	CF ₃ CH ₂ -	H	-CH ₂ F	N
	225	Et	n-Bu	CF ₃ CH ₂ -	H	-CH ₂ F	N
	226	n-Pr	n-Pr	CF ₃ CH ₂ -	H	-CH ₂ F	N
10	227	H	Me	H	H	-CH ₂ F	C
	228	H	Et	H	H	-CH ₂ F	C
	229	H	n-Pr	H	H	-CH ₂ F	C
15	230	H	i-Pr	H	H	-CH ₂ F	C
	231	H	n-Bu	H	H	-CH ₂ F	C
	232	H	Me	H	H	-CH ₂ F	N
20	233	H	Et	H	H	-CH ₂ F	N
	234	H	n-Pr	H	H	-CH ₂ F	N
	235	H	i-Pr	H	H	-CH ₂ F	N
25	236	H	n-Bu	H	H	-CH ₂ F	N
	237	Me	Me	H	H	-CH ₂ F	C
	238	Me	Et	H	H	-CH ₂ F	C
30	239	Me	n-Pr	H	H	-CH ₂ F	C
	240	Me	i-Pr	H	H	-CH ₂ F	C
	241	Me	n-Bu	H	H	-CH ₂ F	C
35	242	Et	Et	H	H	-CH ₂ F	C
	243	Et	n-Pr	H	H	-CH ₂ F	C
	244	Et	i-Pr	H	H	-CH ₂ F	C
40	245	Et	n-Bu	H	H	-CH ₂ F	C
	246	n-Pr	n-Pr	H	H	-CH ₂ F	C
	247	Me	Me	H	H	-CH ₂ F	N
45	248	Me	Et	H	H	-CH ₂ F	N
	249	Me	n-Pr	H	H	-CH ₂ F	N
	250	Me	i-Pr	H	H	-CH ₂ F	N
50	251	Me	n-Bu	H	H	-CH ₂ F	N
	252	Et	Et	H	H	-CH ₂ F	N
	253	Et	n-Pr	H	H	-CH ₂ F	N
55	254	Et	i-Pr	H	H	-CH ₂ F	N
	255	Et	n-Bu	H	H	-CH ₂ F	N
	256	n-Pr	n-Pr	H	H	-CH ₂ F	N
	257	H	Ph	CF ₃ CH ₂ -	CF ₃ CH ₂ -	-CH ₂ F	C
	258	H	Ph	H	CF ₃ CH ₂ -	-CH ₂ F	C
	259	H	Ph	Me	CF ₃ CH ₂ -	-CH ₂ F	C
	260	H	Ph	H	H	-CH ₂ F	C
	261	H	Ph	CF ₃ CH ₂ -	CF ₃ CH ₂ -	-CH ₂ F	N

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5	262	H	Ph	Me	CF ₃ CH ₂ -	-CH ₂ F	N
	263	H	Ph	H	CF ₃ CH ₂ -	-CH ₂ F	N
	264	H	Ph	H	H	-CH ₂ F	N
	265	Me	Ph	CF ₃ CH ₂ -	CF ₃ CH ₂ -	-CH ₂ F	C
	266	Me	Ph	Me	CF ₃ CH ₂ -	-CH ₂ F	C
10	267	Me	Ph	H	CF ₃ CH ₂ -	-CH ₂ F	C
	268	Me	Ph	H	H	-CH ₂ F	C
	269	Me	Ph	CF ₃ CH ₂ -	CF ₃ CH ₂ -	-CH ₂ F	N
	270	Me	Ph	Me	CF ₃ CH ₂ -	-CH ₂ F	N
	271	Me	Ph	H	CF ₃ CH ₂ -	-CH ₂ F	N
15	272	Me	Ph	H	H	-CH ₂ F	N
	273	H	Me	CF ₃ CH ₂ -	CF ₃ CH ₂ -	-CH ₂ OH	C
	274	H	Et	CF ₃ CH ₂ -	CF ₃ CH ₂ -	-CH ₂ OH	C
	275	H	n-Pr	CF ₃ CH ₂ -	CF ₃ CH ₂ -	-CH ₂ OH	C
	276	H	i-Pr	CF ₃ CH ₂ -	CF ₃ CH ₂ -	-CH ₂ OH	C
20	277	H	n-Bu	CF ₃ CH ₂ -	CF ₃ CH ₂ -	-CH ₂ OH	C
	278	H	Me	CF ₃ CH ₂ -	CF ₃ CH ₂ -	-CH ₂ OH	N
	279	H	Et	CF ₃ CH ₂ -	CF ₃ CH ₂ -	-CH ₂ OH	N
	280	H	n-Pr	CF ₃ CH ₂ -	CF ₃ CH ₂ -	-CH ₂ OH	N
	281	H	i-Pr	CF ₃ CH ₂ -	CF ₃ CH ₂ -	-CH ₂ OH	N
25	282	H	n-Bu	CF ₃ CH ₂ -	CF ₃ CH ₂ -	-CH ₂ OH	N
	283	Me	Me	CF ₃ CH ₂ -	CF ₃ CH ₂ -	-CH ₂ OH	C
	284	Me	Et	CF ₃ CH ₂ -	CF ₃ CH ₂ -	-CH ₂ OH	C
	285	Me	n-Pr	CF ₃ CH ₂ -	CF ₃ CH ₂ -	-CH ₂ OH	C
	286	Me	i-Pr	CF ₃ CH ₂ -	CF ₃ CH ₂ -	-CH ₂ OH	C
30	287	Me	n-Bu	CF ₃ CH ₂ -	CF ₃ CH ₂ -	-CH ₂ OH	C
	288	Et	Et	CF ₃ CH ₂ -	CF ₃ CH ₂ -	-CH ₂ OH	C
	289	Et	n-Pr	CF ₃ CH ₂ -	CF ₃ CH ₂ -	-CH ₂ OH	C
	290	Et	i-Pr	CF ₃ CH ₂ -	CF ₃ CH ₂ -	-CH ₂ OH	C
	291	Et	n-Bu	CF ₃ CH ₂ -	CF ₃ CH ₂ -	-CH ₂ OH	C
35	292	n-Pr	n-Pr	CF ₃ CH ₂ -	CF ₃ CH ₂ -	-CH ₂ OH	C
	293	Me	Me	CF ₃ CH ₂ -	CF ₃ CH ₂ -	-CH ₂ OH	N
	294	Me	Et	CF ₃ CH ₂ -	CF ₃ CH ₂ -	-CH ₂ OH	N
	295	Me	n-Pr	CF ₃ CH ₂ -	CF ₃ CH ₂ -	-CH ₂ OH	N
	296	Me	i-Pr	CF ₃ CH ₂ -	CF ₃ CH ₂ -	-CH ₂ OH	N
40	297	Me	n-Bu	CF ₃ CH ₂ -	CF ₃ CH ₂ -	-CH ₂ OH	N
	298	Et	Et	CF ₃ CH ₂ -	CF ₃ CH ₂ -	-CH ₂ OH	N
	299	Et	n-Pr	CF ₃ CH ₂ -	CF ₃ CH ₂ -	-CH ₂ OH	N

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	300	Et	i-Pr	CF ₃ CH ₂ -	CF ₃ CH ₂ -	-CH ₂ OH	N
	301	Et	n-Bu	CF ₃ CH ₂ -	CF ₃ CH ₂ -	-CH ₂ OH	N
5	302	n-Pr	n-Pr	CF ₃ CH ₂ -	CF ₃ CH ₂ -	-CH ₂ OH	N
	303	H	Me	Me	CF ₃ CH ₂ -	-CH ₂ OH	C
	304	H	Et	Me	CF ₃ CH ₂ -	-CH ₂ OH	C
	305	H	n-Pr	Me	CF ₃ CH ₂ -	-CH ₂ OH	C
10	306	H	i-Pr	Me	CF ₃ CH ₂ -	-CH ₂ OH	C
	307	H	n-Bu	Me	CF ₃ CH ₂ -	-CH ₂ OH	C
	308	H	Me	Me	CF ₃ CH ₂ -	-CH ₂ OH	N
15	309	H	Et	Me	CF ₃ CH ₂ -	-CH ₂ OH	N
	310	H	n-Pr	Me	CF ₃ CH ₂ -	-CH ₂ OH	N
	311	H	i-Pr	Me	CF ₃ CH ₂ -	-CH ₂ OH	N
	312	H	n-Bu	Me	CF ₃ CH ₂ -	-CH ₂ OH	N
20	313	Me	Me	Me	CF ₃ CH ₂ -	-CH ₂ OH	C
	314	Me	Et	Me	CF ₃ CH ₂ -	-CH ₂ OH	C
	315	Me	n-Pr	Me	CF ₃ CH ₂ -	-CH ₂ OH	C
	316	Me	i-Pr	Me	CF ₃ CH ₂ -	-CH ₂ OH	C
25	317	Me	n-Bu	Me	CF ₃ CH ₂ -	-CH ₂ OH	C
	318	Et	Et	Me	CF ₃ CH ₂ -	-CH ₂ OH	C
	319	Et	n-Pr	Me	CF ₃ CH ₂ -	-CH ₂ OH	C
	320	Et	i-Pr	Me	CF ₃ CH ₂ -	-CH ₂ OH	C
30	321	Et	n-Bu	Me	CF ₃ CH ₂ -	-CH ₂ OH	C
	322	n-Pr	n-Pr	Me	CF ₃ CH ₂ -	-CH ₂ OH	C
	323	Me	Me	Me	CF ₃ CH ₂ -	-CH ₂ OH	N
35	324	Me	Et	Me	CF ₃ CH ₂ -	-CH ₂ OH	N
	325	Me	n-Pr	Me	CF ₃ CH ₂ -	-CH ₂ OH	N
	326	Me	i-Pr	Me	CF ₃ CH ₂ -	-CH ₂ OH	N
	327	Me	n-Bu	Me	CF ₃ CH ₂ -	-CH ₂ OH	N
40	328	Et	Et	Me	CF ₃ CH ₂ -	-CH ₂ OH	N
	329	Et	n-Pr	Me	CF ₃ CH ₂ -	-CH ₂ OH	N
	330	Et	i-Pr	Me	CF ₃ CH ₂ -	-CH ₂ OH	N
	331	Et	n-Bu	Me	CF ₃ CH ₂ -	-CH ₂ OH	N
45	332	n-Pr	n-Pr	Me	CF ₃ CH ₂ -	-CH ₂ OH	N
	333	H	Me	CF ₃ CH ₂ -	H	-CH ₂ OH	C
	334	H	Et	CF ₃ CH ₂ -	H	-CH ₂ OH	C
50	335	H	n-Pr	CF ₃ CH ₂ -	H	-CH ₂ OH	C
	336	H	i-Pr	CF ₃ CH ₂ -	H	-CH ₂ OH	C
	337	H	n-Bu	CF ₃ CH ₂ -	H	-CH ₂ OH	C

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5	338	H	Me	CF ₃ CH ₂ -	H	-CH ₂ OH	N
	339	H	Et	CF ₃ CH ₂ -	H	-CH ₂ OH	N
	340	H	n-Pr	CF ₃ CH ₂ -	H	-CH ₂ OH	N
	341	H	i-Pr	CF ₃ CH ₂ -	H	-CH ₂ OH	N
	342	H	n-Bu	CF ₃ CH ₂ -	H	-CH ₂ OH	N
10	343	Me	Me	CF ₃ CH ₂ -	H	-CH ₂ OH	C
	344	Me	Et	CF ₃ CH ₂ -	H	-CH ₂ OH	C
	345	Me	n-Pr	CF ₃ CH ₂ -	H	-CH ₂ OH	C
	346	Me	i-Pr	CF ₃ CH ₂ -	H	-CH ₂ OH	C
15	347	Me	n-Bu	CF ₃ CH ₂ -	H	-CH ₂ OH	C
	348	Et	Et	CF ₃ CH ₂ -	H	-CH ₂ OH	C
	349	Et	n-Pr	CF ₃ CH ₂ -	H	-CH ₂ OH	C
	350	Et	i-Pr	CF ₃ CH ₂ -	H	-CH ₂ OH	C
20	351	Et	n-Bu	CF ₃ CH ₂ -	H	-CH ₂ OH	C
	352	n-Pr	n-Pr	CF ₃ CH ₂ -	H	-CH ₂ OH	C
	353	Me	Me	CF ₃ CH ₂ -	H	-CH ₂ OH	N
	354	Me	Et	CF ₃ CH ₂ -	H	-CH ₂ OH	N
25	355	Me	n-Pr	CF ₃ CH ₂ -	H	-CH ₂ OH	N
	356	Me	i-Pr	CF ₃ CH ₂ -	H	-CH ₂ OH	N
	357	Me	n-Bu	CF ₃ CH ₂ -	H	-CH ₂ OH	N
	358	Et	Et	CF ₃ CH ₂ -	H	-CH ₂ OH	N
30	359	Et	n-Pr	CF ₃ CH ₂ -	H	-CH ₂ OH	N
	360	Et	i-Pr	CF ₃ CH ₂ -	H	-CH ₂ OH	N
	361	Et	n-Bu	CF ₃ CH ₂ -	H	-CH ₂ OH	N
	362	n-Pr	n-Pr	CF ₃ CH ₂ -	H	-CH ₂ OH	N
35	363	H	Me	H	H	-CH ₂ OH	C
	364	H	Et	H	H	-CH ₂ OH	C
	365	H	n-Pr	H	H	-CH ₂ OH	C
	366	H	i-Pr	H	H	-CH ₂ OH	C
40	367	H	n-Bu	H	H	-CH ₂ OH	C
	368	H	Me	H	H	-CH ₂ OH	N
	369	H	Et	H	H	-CH ₂ OH	N
	370	H	n-Pr	H	H	-CH ₂ OH	N
45	371	H	i-Pr	H	H	-CH ₂ OH	N
	372	H	n-Bu	H	H	-CH ₂ OH	N
	373	Me	Me	H	H	-CH ₂ OH	C
	374	Me	Et	H	H	-CH ₂ OH	C
50	375	Me	n-Pr	H	H	-CH ₂ OH	C

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5	376	Me	i-Pr	H	H	-CH ₂ OH	C
	377	Me	n-Bu	H	H	-CH ₂ OH	C
	378	Et	Et	H	H	-CH ₂ OH	C
	379	Et	n-Pr	H	H	-CH ₂ OH	C
	380	Et	i-Pr	H	H	-CH ₂ OH	C
10	381	Et	n-Bu	H	H	-CH ₂ OH	C
	382	n-Pr	n-Pr	H	H	-CH ₂ OH	C
	383	Me	Me	H	H	-CH ₂ OH	N
15	384	Me	Et	H	H	-CH ₂ OH	N
	385	Me	n-Pr	H	H	-CH ₂ OH	N
	386	Me	i-Pr	H	H	-CH ₂ OH	N
	387	Me	n-Bu	H	H	-CH ₂ OH	N
20	388	Et	Et	H	H	-CH ₂ OH	N
	389	Et	n-Pr	H	H	-CH ₂ OH	N
	390	Et	i-Pr	H	H	-CH ₂ OH	N
	391	Et	n-Bu	H	H	-CH ₂ OH	N
25	392	n-Pr	n-Pr	H	H	-CH ₂ OH	N
	393	H	Ph	CF ₃ CH ₂ -	CF ₃ CH ₂ -	-CH ₂ OH	C
	394	H	Ph	H	CF ₃ CH ₂ -	-CH ₂ OH	C
	395	H	Ph	Me	CF ₃ CH ₂ -	-CH ₂ OH	C
30	396	H	Ph	H	H	-CH ₂ OH	C
	397	H	Ph	CF ₃ CH ₂ -	CF ₃ CH ₂ -	-CH ₂ OH	N
	398	H	Ph	Me	CF ₃ CH ₂ -	-CH ₂ OH	N
	399	H	Ph	H	CF ₃ CH ₂ -	-CH ₂ OH	N
35	400	H	Ph	H	H	-CH ₂ OH	N
	401	Me	Ph	CF ₃ CH ₂ -	CF ₃ CH ₂ -	-CH ₂ OH	C
	402	Me	Ph	Me	CF ₃ CH ₂ -	-CH ₂ OH	C
40	403	Me	Ph	H	CF ₃ CH ₂ -	-CH ₂ OH	C
	404	Me	Ph	H	H	-CH ₂ OH	C
	405	Me	Ph	CF ₃ CH ₂ -	CF ₃ CH ₂ -	-CH ₂ OH	N
	406	Me	Ph	Me	CF ₃ CH ₂ -	-CH ₂ OH	N
45	407	Me	Ph	H	CF ₃ CH ₂ -	-CH ₂ OH	N
	408	Me	Ph	H	H	-CH ₂ OH	N
	409	H	Me	-CH ₂ OCO-t-Bu	-CH ₂ OCO-t-Bu	Me	C
50	410	H	Et	-CH ₂ OCO-t-Bu	-CH ₂ OCO-t-Bu	Me	C
	411	H	n-Pr	-CH ₂ OCO-t-Bu	-CH ₂ OCO-t-Bu	Me	C
	412	H	i-Pr	-CH ₂ OCO-t-Bu	-CH ₂ OCO-t-Bu	Me	C
	413	H	n-Bu	-CH ₂ OCO-t-Bu	-CH ₂ OCO-t-Bu	Me	C

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	414	H	Me	-CH ₂ OCO-t-Bu	-CH ₂ OCO-t-Bu	Me	N
	415	H	Et	-CH ₂ OCO-t-Bu	-CH ₂ OCO-t-Bu	Me	N
5	416	H	n-Pr	-CH ₂ OCO-t-Bu	-CH ₂ OCO-t-Bu	Me	N
	417	H	i-Pr	-CH ₂ OCO-t-Bu	-CH ₂ OCO-t-Bu	Me	N
	418	H	n-Bu	-CH ₂ OCO-t-Bu	-CH ₂ OCO-t-Bu	Me	N
	419	Me	Me	-CH ₂ OCO-t-Bu	-CH ₂ OCO-t-Bu	Me	C
10	420	Me	Et	-CH ₂ OCO-t-Bu	-CH ₂ OCO-t-Bu	Me	C
	421	Me	n-Pr	-CH ₂ OCO-t-Bu	-CH ₂ OCO-t-Bu	Me	C
	422	Me	i-Pr	-CH ₂ OCO-t-Bu	-CH ₂ OCO-t-Bu	Me	C
15	423	Me	n-Bu	-CH ₂ OCO-t-Bu	-CH ₂ OCO-t-Bu	Me	C
	424	Et	Et	-CH ₂ OCO-t-Bu	-CH ₂ OCO-t-Bu	Me	C
	425	Et	n-Pr	-CH ₂ OCO-t-Bu	-CH ₂ OCO-t-Bu	Me	C
	426	Et	i-Pr	-CH ₂ OCO-t-Bu	-CH ₂ OCO-t-Bu	Me	C
20	427	Et	n-Bu	-CH ₂ OCO-t-Bu	-CH ₂ OCO-t-Bu	Me	C
	428	n-Pr	n-Pr	-CH ₂ OCO-t-Bu	-CH ₂ OCO-t-Bu	Me	C
	429	Me	Me	-CH ₂ OCO-t-Bu	-CH ₂ OCO-t-Bu	Me	N
	430	Me	Et	-CH ₂ OCO-t-Bu	-CH ₂ OCO-t-Bu	Me	N
25	431	Me	n-Pr	-CH ₂ OCO-t-Bu	-CH ₂ OCO-t-Bu	Me	N
	432	Me	i-Pr	-CH ₂ OCO-t-Bu	-CH ₂ OCO-t-Bu	Me	N
	433	Me	n-Bu	-CH ₂ OCO-t-Bu	-CH ₂ OCO-t-Bu	Me	N
30	434	Et	Et	-CH ₂ OCO-t-Bu	-CH ₂ OCO-t-Bu	Me	N
	435	Et	n-Pr	-CH ₂ OCO-t-Bu	-CH ₂ OCO-t-Bu	Me	N
	436	Et	i-Pr	-CH ₂ OCO-t-Bu	-CH ₂ OCO-t-Bu	Me	N
	437	Et	n-Bu	-CH ₂ OCO-t-Bu	-CH ₂ OCO-t-Bu	Me	N
35	438	n-Pr	n-Pr	-CH ₂ OCO-t-Bu	-CH ₂ OCO-t-Bu	Me	N
	439	H	Me	-CH ₂ OCO-t-Bu	-CH ₂ OCO-t-Bu	-CH ₂ F	C
	440	H	Et	-CH ₂ OCO-t-Bu	-CH ₂ OCO-t-Bu	-CH ₂ F	C
40	441	H	n-Pr	-CH ₂ OCO-t-Bu	-CH ₂ OCO-t-Bu	-CH ₂ F	C
	442	H	i-Pr	-CH ₂ OCO-t-Bu	-CH ₂ OCO-t-Bu	-CH ₂ F	C
	443	H	n-Bu	-CH ₂ OCO-t-Bu	-CH ₂ OCO-t-Bu	-CH ₂ F	C
	444	H	Me	-CH ₂ OCO-t-Bu	-CH ₂ OCO-t-Bu	-CH ₂ F	N
45	445	H	Et	-CH ₂ OCO-t-Bu	-CH ₂ OCO-t-Bu	-CH ₂ F	N
	446	H	n-Pr	-CH ₂ OCO-t-Bu	-CH ₂ OCO-t-Bu	-CH ₂ F	N
	447	H	i-Pr	-CH ₂ OCO-t-Bu	-CH ₂ OCO-t-Bu	-CH ₂ F	N
	448	H	n-Bu	-CH ₂ OCO-t-Bu	-CH ₂ OCO-t-Bu	-CH ₂ F	N
50	449	Me	Me	-CH ₂ OCO-t-Bu	-CH ₂ OCO-t-Bu	-CH ₂ F	C
	450	Me	Et	-CH ₂ OCO-t-Bu	-CH ₂ OCO-t-Bu	-CH ₂ F	C
	451	Me	n-Pr	-CH ₂ OCO-t-Bu	-CH ₂ OCO-t-Bu	-CH ₂ F	C

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5	452	Me	i-Pr	-CH ₂ OCO-t-Bu	-CH ₂ OCO-t-Bu	-CH ₂ F	C
	453	Me	n-Bu	-CH ₂ OCO-t-Bu	-CH ₂ OCO-t-Bu	-CH ₂ F	C
	454	Et	Et	-CH ₂ OCO-t-Bu	-CH ₂ OCO-t-Bu	-CH ₂ F	C
	455	Et	n-Pr	-CH ₂ OCO-t-Bu	-CH ₂ OCO-t-Bu	-CH ₂ F	C
	456	Et	i-Pr	-CH ₂ OCO-t-Bu	-CH ₂ OCO-t-Bu	-CH ₂ F	C
10	457	Et	n-Bu	-CH ₂ OCO-t-Bu	-CH ₂ OCO-t-Bu	-CH ₂ F	C
	458	n-Pr	n-Pr	-CH ₂ OCO-t-Bu	-CH ₂ OCO-t-Bu	-CH ₂ F	C
	459	Me	Me	-CH ₂ OCO-t-Bu	-CH ₂ OCO-t-Bu	-CH ₂ F	N
	460	Me	Et	-CH ₂ OCO-t-Bu	-CH ₂ OCO-t-Bu	-CH ₂ F	N
	461	Me	n-Pr	-CH ₂ OCO-t-Bu	-CH ₂ OCO-t-Bu	-CH ₂ F	N
15	462	Me	i-Pr	-CH ₂ OCO-t-Bu	-CH ₂ OCO-t-Bu	-CH ₂ F	N
	463	Me	n-Bu	-CH ₂ OCO-t-Bu	-CH ₂ OCO-t-Bu	-CH ₂ F	N
	464	Et	Et	-CH ₂ OCO-t-Bu	-CH ₂ OCO-t-Bu	-CH ₂ F	N
	465	Et	n-Pr	-CH ₂ OCO-t-Bu	-CH ₂ OCO-t-Bu	-CH ₂ F	N
	466	Et	i-Pr	-CH ₂ OCO-t-Bu	-CH ₂ OCO-t-Bu	-CH ₂ F	N
20	467	Et	n-Bu	-CH ₂ OCO-t-Bu	-CH ₂ OCO-t-Bu	-CH ₂ F	N
	468	n-Pr	n-Pr	-CH ₂ OCO-t-Bu	-CH ₂ OCO-t-Bu	-CH ₂ F	N
	469	H	Me	-CH ₂ OCO-t-Bu	-CH ₂ OCO-t-Bu	-CH ₂ OH	C
	470	H	Et	-CH ₂ OCO-t-Bu	-CH ₂ OCO-t-Bu	-CH ₂ OH	C
	471	H	n-Pr	-CH ₂ OCO-t-Bu	-CH ₂ OCO-t-Bu	-CH ₂ OH	C
30	472	H	i-Pr	-CH ₂ OCO-t-Bu	-CH ₂ OCO-t-Bu	-CH ₂ OH	C
	473	H	n-Bu	-CH ₂ OCO-t-Bu	-CH ₂ OCO-t-Bu	-CH ₂ OH	C
	474	H	Me	-CH ₂ OCO-t-Bu	-CH ₂ OCO-t-Bu	-CH ₂ OH	N
	475	H	Et	-CH ₂ OCO-t-Bu	-CH ₂ OCO-t-Bu	-CH ₂ OH	N
	476	H	n-Pr	-CH ₂ OCO-t-Bu	-CH ₂ OCO-t-Bu	-CH ₂ OH	N
35	477	H	i-Pr	-CH ₂ OCO-t-Bu	-CH ₂ OCO-t-Bu	-CH ₂ OH	N
	478	H	n-Bu	-CH ₂ OCO-t-Bu	-CH ₂ OCO-t-Bu	-CH ₂ OH	N
	479	Me	Me	-CH ₂ OCO-t-Bu	-CH ₂ OCO-t-Bu	-CH ₂ OH	C
	480	Me	Et	-CH ₂ OCO-t-Bu	-CH ₂ OCO-t-Bu	-CH ₂ OH	C
	481	Me	n-Pr	-CH ₂ OCO-t-Bu	-CH ₂ OCO-t-Bu	-CH ₂ OH	C
45	482	Me	i-Pr	-CH ₂ OCO-t-Bu	-CH ₂ OCO-t-Bu	-CH ₂ OH	C
	483	Me	n-Bu	-CH ₂ OCO-t-Bu	-CH ₂ OCO-t-Bu	-CH ₂ OH	C
	484	Et	Et	-CH ₂ OCO-t-Bu	-CH ₂ OCO-t-Bu	-CH ₂ OH	C
	485	Et	n-Pr	-CH ₂ OCO-t-Bu	-CH ₂ OCO-t-Bu	-CH ₂ OH	C
	486	Et	i-Pr	-CH ₂ OCO-t-Bu	-CH ₂ OCO-t-Bu	-CH ₂ OH	C
50	487	Et	n-Bu	-CH ₂ OCO-t-Bu	-CH ₂ OCO-t-Bu	-CH ₂ OH	C
	488	n-Pr	n-Pr	-CH ₂ OCO-t-Bu	-CH ₂ OCO-t-Bu	-CH ₂ OH	C
	489	Me	Me	-CH ₂ OCO-t-Bu	-CH ₂ OCO-t-Bu	-CH ₂ OH	N

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	490	Me	Et	-CH ₂ OCO-t-Bu	-CH ₂ OCO-t-Bu	-CH ₂ OH	N
	491	Me	n-Pr	-CH ₂ OCO-t-Bu	-CH ₂ OCO-t-Bu	-CH ₂ OH	N
5	492	Me	i-Pr	-CH ₂ OCO-t-Bu	-CH ₂ OCO-t-Bu	-CH ₂ OH	N
	493	Me	n-Bu	-CH ₂ OCO-t-Bu	-CH ₂ OCO-t-Bu	-CH ₂ OH	N
	494	Et	Et	-CH ₂ OCO-t-Bu	-CH ₂ OCO-t-Bu	-CH ₂ OH	N
	495	Et	n-Pr	-CH ₂ OCO-t-Bu	-CH ₂ OCO-t-Bu	-CH ₂ OH	N
10	496	Et	i-Pr	-CH ₂ OCO-t-Bu	-CH ₂ OCO-t-Bu	-CH ₂ OH	N
	497	Et	n-Bu	-CH ₂ OCO-t-Bu	-CH ₂ OCO-t-Bu	-CH ₂ OH	N
	498	n-Pr	n-Pr	-CH ₂ OCO-t-Bu	-CH ₂ OCO-t-Bu	-CH ₂ OH	N
	499	H	Me	-CH ₂ CH ₂ S-CO-i-Pr	-CH ₂ CH ₂ S-CO-i-Pr	Me	C
15	500	H	Et	-CH ₂ CH ₂ S-CO-i-Pr	-CH ₂ CH ₂ S-CO-i-Pr	Me	C
	501	H	n-Pr	-CH ₂ CH ₂ S-CO-i-Pr	-CH ₂ CH ₂ S-CO-i-Pr	Me	C
	502	H	i-Pr	-CH ₂ CH ₂ S-CO-i-Pr	-CH ₂ CH ₂ S-CO-i-Pr	Me	C
20	503	H	n-Bu	-CH ₂ CH ₂ S-CO-i-Pr	-CH ₂ CH ₂ S-CO-i-Pr	Me	C
	504	H	Me	-CH ₂ CH ₂ S-CO-i-Pr	-CH ₂ CH ₂ S-CO-i-Pr	Me	N
	505	H	Et	-CH ₂ CH ₂ S-CO-i-Pr	-CH ₂ CH ₂ S-CO-i-Pr	Me	N
	506	H	n-Pr	-CH ₂ CH ₂ S-CO-i-Pr	-CH ₂ CH ₂ S-CO-i-Pr	Me	N
25	507	H	i-Pr	-CH ₂ CH ₂ S-CO-i-Pr	-CH ₂ CH ₂ S-CO-i-Pr	Me	N
	508	H	n-Bu	-CH ₂ CH ₂ S-CO-i-Pr	-CH ₂ CH ₂ S-CO-i-Pr	Me	N
	509	Me	Me	-CH ₂ CH ₂ S-CO-i-Pr	-CH ₂ CH ₂ S-CO-i-Pr	Me	C
	510	Me	Et	-CH ₂ CH ₂ S-CO-i-Pr	-CH ₂ CH ₂ S-CO-i-Pr	Me	C
30	511	Me	n-Pr	-CH ₂ CH ₂ S-CO-i-Pr	-CH ₂ CH ₂ S-CO-i-Pr	Me	C
	512	Me	i-Pr	-CH ₂ CH ₂ S-CO-i-Pr	-CH ₂ CH ₂ S-CO-i-Pr	Me	C
	513	Me	n-Bu	-CH ₂ CH ₂ S-CO-i-Pr	-CH ₂ CH ₂ S-CO-i-Pr	Me	C
35	514	Et	Et	-CH ₂ CH ₂ S-CO-i-Pr	-CH ₂ CH ₂ S-CO-i-Pr	Me	C
	515	Et	n-Pr	-CH ₂ CH ₂ S-CO-i-Pr	-CH ₂ CH ₂ S-CO-i-Pr	Me	C
	516	Et	i-Pr	-CH ₂ CH ₂ S-CO-i-Pr	-CH ₂ CH ₂ S-CO-i-Pr	Me	C
	517	Et	n-Bu	-CH ₂ CH ₂ S-CO-i-Pr	-CH ₂ CH ₂ S-CO-i-Pr	Me	C
40	518	n-Pr	n-Pr	-CH ₂ CH ₂ S-CO-i-Pr	-CH ₂ CH ₂ S-CO-i-Pr	Me	C
	519	Me	Me	-CH ₂ CH ₂ S-CO-i-Pr	-CH ₂ CH ₂ S-CO-i-Pr	Me	N
	520	Me	Et	-CH ₂ CH ₂ S-CO-i-Pr	-CH ₂ CH ₂ S-CO-i-Pr	Me	N
	521	Me	n-Pr	-CH ₂ CH ₂ S-CO-i-Pr	-CH ₂ CH ₂ S-CO-i-Pr	Me	N
45	522	Me	i-Pr	-CH ₂ CH ₂ S-CO-i-Pr	-CH ₂ CH ₂ S-CO-i-Pr	Me	N
	523	Me	n-Bu	-CH ₂ CH ₂ S-CO-i-Pr	-CH ₂ CH ₂ S-CO-i-Pr	Me	N
	524	Et	Et	-CH ₂ CH ₂ S-CO-i-Pr	-CH ₂ CH ₂ S-CO-i-Pr	Me	N
50	525	Et	n-Pr	-CH ₂ CH ₂ S-CO-i-Pr	-CH ₂ CH ₂ S-CO-i-Pr	Me	N
	526	Et	i-Pr	-CH ₂ CH ₂ S-CO-i-Pr	-CH ₂ CH ₂ S-CO-i-Pr	Me	N
	527	Et	n-Bu	-CH ₂ CH ₂ S-CO-i-Pr	-CH ₂ CH ₂ S-CO-i-Pr	Me	N
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	528	n-Pr	n-Pr	-CH ₂ CH ₂ S-CO-i-Pr	-CH ₂ CH ₂ S-CO-i-Pr	Me	N
	529	H	Me	-CH ₂ CH ₂ S-CO-i-Pr	-CH ₂ CH ₂ S-CO-i-Pr	-CH ₂ F	C
5	530	H	Et	-CH ₂ CH ₂ S-CO-i-Pr	-CH ₂ CH ₂ S-CO-i-Pr	-CH ₂ F	C
	531	H	n-Pr	-CH ₂ CH ₂ S-CO-i-Pr	-CH ₂ CH ₂ S-CO-i-Pr	-CH ₂ F	C
	532	H	i-Pr	-CH ₂ CH ₂ S-CO-i-Pr	-CH ₂ CH ₂ S-CO-i-Pr	-CH ₂ F	C
	533	H	n-Bu	-CH ₂ CH ₂ S-CO-i-Pr	-CH ₂ CH ₂ S-CO-i-Pr	-CH ₂ F	C
10	534	H	Me	-CH ₂ CH ₂ S-CO-i-Pr	-CH ₂ CH ₂ S-CO-i-Pr	-CH ₂ F	N
	535	H	Et	-CH ₂ CH ₂ S-CO-i-Pr	-CH ₂ CH ₂ S-CO-i-Pr	-CH ₂ F	N
	536	H	n-Pr	-CH ₂ CH ₂ S-CO-i-Pr	-CH ₂ CH ₂ S-CO-i-Pr	-CH ₂ F	N
15	537	H	i-Pr	-CH ₂ CH ₂ S-CO-i-Pr	-CH ₂ CH ₂ S-CO-i-Pr	-CH ₂ F	N
	538	H	n-Bu	-CH ₂ CH ₂ S-CO-i-Pr	-CH ₂ CH ₂ S-CO-i-Pr	-CH ₂ F	N
	539	Me	Me	-CH ₂ CH ₂ S-CO-i-Pr	-CH ₂ CH ₂ S-CO-i-Pr	-CH ₂ F	C
	540	Me	Et	-CH ₂ CH ₂ S-CO-i-Pr	-CH ₂ CH ₂ S-CO-i-Pr	-CH ₂ F	C
20	541	Me	n-Pr	-CH ₂ CH ₂ S-CO-i-Pr	-CH ₂ CH ₂ S-CO-i-Pr	-CH ₂ F	C
	542	Me	i-Pr	-CH ₂ CH ₂ S-CO-i-Pr	-CH ₂ CH ₂ S-CO-i-Pr	-CH ₂ F	C
	543	Me	n-Bu	-CH ₂ CH ₂ S-CO-i-Pr	-CH ₂ CH ₂ S-CO-i-Pr	-CH ₂ F	C
	544	Et	Et	-CH ₂ CH ₂ S-CO-i-Pr	-CH ₂ CH ₂ S-CO-i-Pr	-CH ₂ F	C
25	545	Et	n-Pr	-CH ₂ CH ₂ S-CO-i-Pr	-CH ₂ CH ₂ S-CO-i-Pr	-CH ₂ F	C
	546	Et	i-Pr	-CH ₂ CH ₂ S-CO-i-Pr	-CH ₂ CH ₂ S-CO-i-Pr	-CH ₂ F	C
	547	Et	n-Bu	-CH ₂ CH ₂ S-CO-i-Pr	-CH ₂ CH ₂ S-CO-i-Pr	-CH ₂ F	C
30	548	n-Pr	n-Pr	-CH ₂ CH ₂ S-CO-i-Pr	-CH ₂ CH ₂ S-CO-i-Pr	-CH ₂ F	C
	549	Me	Me	-CH ₂ CH ₂ S-CO-i-Pr	-CH ₂ CH ₂ S-CO-i-Pr	-CH ₂ F	N
	550	Me	Et	-CH ₂ CH ₂ S-CO-i-Pr	-CH ₂ CH ₂ S-CO-i-Pr	-CH ₂ F	N
	551	Me	n-Pr	-CH ₂ CH ₂ S-CO-i-Pr	-CH ₂ CH ₂ S-CO-i-Pr	-CH ₂ F	N
35	552	Me	i-Pr	-CH ₂ CH ₂ S-CO-i-Pr	-CH ₂ CH ₂ S-CO-i-Pr	-CH ₂ F	N
	553	Me	n-Bu	-CH ₂ CH ₂ S-CO-i-Pr	-CH ₂ CH ₂ S-CO-i-Pr	-CH ₂ F	N
	554	Et	Et	-CH ₂ CH ₂ S-CO-i-Pr	-CH ₂ CH ₂ S-CO-i-Pr	-CH ₂ F	N
	555	Et	n-Pr	-CH ₂ CH ₂ S-CO-i-Pr	-CH ₂ CH ₂ S-CO-i-Pr	-CH ₂ F	N
40	556	Et	i-Pr	-CH ₂ CH ₂ S-CO-i-Pr	-CH ₂ CH ₂ S-CO-i-Pr	-CH ₂ F	N
	557	Et	n-Bu	-CH ₂ CH ₂ S-CO-i-Pr	-CH ₂ CH ₂ S-CO-i-Pr	-CH ₂ F	N
	558	n-Pr	n-Pr	-CH ₂ CH ₂ S-CO-i-Pr	-CH ₂ CH ₂ S-CO-i-Pr	-CH ₂ F	N
45	559	H	Me	-CH ₂ CH ₂ S-CO-i-Pr	-CH ₂ CH ₂ S-CO-i-Pr	-CH ₂ OH	C
	560	H	Et	-CH ₂ CH ₂ S-CO-i-Pr	-CH ₂ CH ₂ S-CO-i-Pr	-CH ₂ OH	C
	561	H	n-Pr	-CH ₂ CH ₂ S-CO-i-Pr	-CH ₂ CH ₂ S-CO-i-Pr	-CH ₂ OH	C
	562	H	i-Pr	-CH ₂ CH ₂ S-CO-i-Pr	-CH ₂ CH ₂ S-CO-i-Pr	-CH ₂ OH	C
50	563	H	n-Bu	-CH ₂ CH ₂ S-CO-i-Pr	-CH ₂ CH ₂ S-CO-i-Pr	-CH ₂ OH	C
	564	H	Me	-CH ₂ CH ₂ S-CO-i-Pr	-CH ₂ CH ₂ S-CO-i-Pr	-CH ₂ OH	N
	565	H	Et	-CH ₂ CH ₂ S-CO-i-Pr	-CH ₂ CH ₂ S-CO-i-Pr	-CH ₂ OH	N

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5	566	H	n-Pr	-CH ₂ CH ₂ S-CO-i-Pr	-CH ₂ CH ₂ S-CO-i-Pr	-CH ₂ OH	N
	567	H	i-Pr	-CH ₂ CH ₂ S-CO-i-Pr	-CH ₂ CH ₂ S-CO-i-Pr	-CH ₂ OH	N
	568	H	n-Bu	-CH ₂ CH ₂ S-CO-i-Pr	-CH ₂ CH ₂ S-CO-i-Pr	-CH ₂ OH	N
	569	Me	Me	-CH ₂ CH ₂ S-CO-i-Pr	-CH ₂ CH ₂ S-CO-i-Pr	-CH ₂ OH	C
	570	Me	Et	-CH ₂ CH ₂ S-CO-i-Pr	-CH ₂ CH ₂ S-CO-i-Pr	-CH ₂ OH	C
10	571	Me	n-Pr	-CH ₂ CH ₂ S-CO-i-Pr	-CH ₂ CH ₂ S-CO-i-Pr	-CH ₂ OH	C
	572	Me	i-Pr	-CH ₂ CH ₂ S-CO-i-Pr	-CH ₂ CH ₂ S-CO-i-Pr	-CH ₂ OH	C
	573	Me	n-Bu	-CH ₂ CH ₂ S-CO-i-Pr	-CH ₂ CH ₂ S-CO-i-Pr	-CH ₂ OH	C
	574	Et	Et	-CH ₂ CH ₂ S-CO-i-Pr	-CH ₂ CH ₂ S-CO-i-Pr	-CH ₂ OH	C
15	575	Et	n-Pr	-CH ₂ CH ₂ S-CO-i-Pr	-CH ₂ CH ₂ S-CO-i-Pr	-CH ₂ OH	C
	576	Et	i-Pr	-CH ₂ CH ₂ S-CO-i-Pr	-CH ₂ CH ₂ S-CO-i-Pr	-CH ₂ OH	C
	577	Et	n-Bu	-CH ₂ CH ₂ S-CO-i-Pr	-CH ₂ CH ₂ S-CO-i-Pr	-CH ₂ OH	C
	578	n-Pr	n-Pr	-CH ₂ CH ₂ S-CO-i-Pr	-CH ₂ CH ₂ S-CO-i-Pr	-CH ₂ OH	C
20	579	Me	Me	-CH ₂ CH ₂ S-CO-i-Pr	-CH ₂ CH ₂ S-CO-i-Pr	-CH ₂ OH	N
	580	Me	Et	-CH ₂ CH ₂ S-CO-i-Pr	-CH ₂ CH ₂ S-CO-i-Pr	-CH ₂ OH	N
	581	Me	n-Pr	-CH ₂ CH ₂ S-CO-i-Pr	-CH ₂ CH ₂ S-CO-i-Pr	-CH ₂ OH	N
	582	Me	i-Pr	-CH ₂ CH ₂ S-CO-i-Pr	-CH ₂ CH ₂ S-CO-i-Pr	-CH ₂ OH	N
25	583	Me	n-Bu	-CH ₂ CH ₂ S-CO-i-Pr	-CH ₂ CH ₂ S-CO-i-Pr	-CH ₂ OH	N
	584	Et	Et	-CH ₂ CH ₂ S-CO-i-Pr	-CH ₂ CH ₂ S-CO-i-Pr	-CH ₂ OH	N
	585	Et	n-Pr	-CH ₂ CH ₂ S-CO-i-Pr	-CH ₂ CH ₂ S-CO-i-Pr	-CH ₂ OH	N
	586	Et	i-Pr	-CH ₂ CH ₂ S-CO-i-Pr	-CH ₂ CH ₂ S-CO-i-Pr	-CH ₂ OH	N
30	587	Et	n-Bu	-CH ₂ CH ₂ S-CO-i-Pr	-CH ₂ CH ₂ S-CO-i-Pr	-CH ₂ OH	N
	588	n-Pr	n-Pr	-CH ₂ CH ₂ S-CO-i-Pr	-CH ₂ CH ₂ S-CO-i-Pr	-CH ₂ OH	N
	589	H	Ph	-CH ₂ OCO-t-Bu	-CH ₂ OCO-t-Bu	Me	C
	590	H	Ph	-CH ₂ OCO-t-Bu	-CH ₂ OCO-t-Bu	-CH ₂ F	C
35	591	H	Ph	-CH ₂ OCO-t-Bu	-CH ₂ OCO-t-Bu	-CH ₂ OH	C
	592	H	Ph	-CH ₂ OCO-t-Bu	-CH ₂ OCO-t-Bu	Me	N
	593	H	Ph	-CH ₂ OCO-t-Bu	-CH ₂ OCO-t-Bu	-CH ₂ F	N
	594	H	Ph	-CH ₂ OCO-t-Bu	-CH ₂ OCO-t-Bu	-CH ₂ OH	N
40	595	Me	Ph	-CH ₂ OCO-t-Bu	-CH ₂ OCO-t-Bu	Me	C
	596	Me	Ph	-CH ₂ OCO-t-Bu	-CH ₂ OCO-t-Bu	-CH ₂ F	C
	597	Me	Ph	-CH ₂ OCO-t-Bu	-CH ₂ OCO-t-Bu	-CH ₂ OH	C
	598	Me	Ph	-CH ₂ OCO-t-Bu	-CH ₂ OCO-t-Bu	Me	N
45	599	Me	Ph	-CH ₂ OCO-t-Bu	-CH ₂ OCO-t-Bu	-CH ₂ F	N
	600	Me	Ph	-CH ₂ OCO-t-Bu	-CH ₂ OCO-t-Bu	-CH ₂ OH	N
	601	H	Ph	-CH ₂ CH ₂ S-CO-i-Pr	-CH ₂ CH ₂ S-CO-i-Pr	Me	C
	602	H	Ph	-CH ₂ CH ₂ S-CO-i-Pr	-CH ₂ CH ₂ S-CO-i-Pr	-CH ₂ F	C
50	603	H	Ph	-CH ₂ CH ₂ S-CO-i-Pr	-CH ₂ CH ₂ S-CO-i-Pr	-CH ₂ OH	C

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	604	H	Ph	-CH ₂ CH ₂ S-CO-i-Pr	-CH ₂ CH ₂ S-CO-i-Pr	Me	N
	605	H	Ph	-CH ₂ CH ₂ S-CO-i-Pr	-CH ₂ CH ₂ S-CO-i-Pr	-CH ₂ F	N
5	606	H	Ph	-CH ₂ CH ₂ S-CO-i-Pr	-CH ₂ CH ₂ S-CO-i-Pr	-CH ₂ OH	N
	607	Me	Ph	-CH ₂ CH ₂ S-CO-i-Pr	-CH ₂ CH ₂ S-CO-i-Pr	Me	C
	608	Me	Ph	-CH ₂ CH ₂ S-CO-i-Pr	-CH ₂ CH ₂ S-CO-i-Pr	-CH ₂ F	C
	609	Me	Ph	-CH ₂ CH ₂ S-CO-i-Pr	-CH ₂ CH ₂ S-CO-i-Pr	-CH ₂ OH	C
10	610	Me	Ph	-CH ₂ CH ₂ S-CO-i-Pr	-CH ₂ CH ₂ S-CO-i-Pr	Me	N
	611	Me	Ph	-CH ₂ CH ₂ S-CO-i-Pr	-CH ₂ CH ₂ S-CO-i-Pr	-CH ₂ F	N
	612	Me	Ph	-CH ₂ CH ₂ S-CO-i-Pr	-CH ₂ CH ₂ S-CO-i-Pr	-CH ₂ OH	N
15	613	H	Ph	CF ₃ CH ₂ -	CF ₃ CH ₂ -	H	C
	614	H	Ph	H	CF ₃ CH ₂ -	H	C
	615	H	Ph	Me	CF ₃ CH ₂ -	H	C
	616	H	Ph	H	H	H	C
20	617	H	Ph	CF ₃ CH ₂ -	CF ₃ CH ₂ -	H	N
	618	H	Ph	Me	CF ₃ CH ₂ -	H	N
	619	H	Ph	H	CF ₃ CH ₂ -	H	N
	620	H	Ph	H	H	H	N
25	621	Me	Ph	CF ₃ CH ₂ -	CF ₃ CH ₂ -	H	C
	622	Me	Ph	Me	CF ₃ CH ₂ -	H	C
	623	Me	Ph	H	CF ₃ CH ₂ -	H	C
	624	Me	Ph	H	H	H	C
30	625	Me	Ph	CF ₃ CH ₂ -	CF ₃ CH ₂ -	H	N
	626	Me	Ph	Me	CF ₃ CH ₂ -	H	N
	627	Me	Ph	H	CF ₃ CH ₂ -	H	N
35	628	Me	Ph	H	H	H	N
	629	H	Me	CF ₃ CH ₂ -	CF ₃ CH ₂ -	Me	C
	630	H	Et	CF ₃ CH ₂ -	CF ₃ CH ₂ -	Me	C
40	631	H	n-Pr	CF ₃ CH ₂ -	CF ₃ CH ₂ -	Me	C
	632	H	i-Pr	CF ₃ CH ₂ -	CF ₃ CH ₂ -	Me	C
	633	H	n-Bu	CF ₃ CH ₂ -	CF ₃ CH ₂ -	Me	C
	634	H	Me	CF ₃ CH ₂ -	CF ₃ CH ₂ -	Me	N
	635	H	Et	CF ₃ CH ₂ -	CF ₃ CH ₂ -	Me	N
45	636	H	n-Pr	CF ₃ CH ₂ -	CF ₃ CH ₂ -	Me	N
	637	H	i-Pr	CF ₃ CH ₂ -	CF ₃ CH ₂ -	Me	N
	638	H	n-Bu	CF ₃ CH ₂ -	CF ₃ CH ₂ -	Me	N
50	639	Me	Me	CF ₃ CH ₂ -	CF ₃ CH ₂ -	Me	C
	640	Me	Et	CF ₃ CH ₂ -	CF ₃ CH ₂ -	Me	C
	641	Me	n-Pr	CF ₃ CH ₂ -	CF ₃ CH ₂ -	Me	C

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5	642	Me	i-Pr	CF ₃ CH ₂ -	CF ₃ CH ₂ -	Me	C
	643	Me	n-Bu	CF ₃ CH ₂ -	CF ₃ CH ₂ -	Me	C
	644	Et	Et	CF ₃ CH ₂ -	CF ₃ CH ₂ -	Me	C
	645	Et	n-Pr	CF ₃ CH ₂ -	CF ₃ CH ₂ -	Me	C
	646	Et	i-Pr	CF ₃ CH ₂ -	CF ₃ CH ₂ -	Me	C
10	647	Et	n-Bu	CF ₃ CH ₂ -	CF ₃ CH ₂ -	Me	C
	648	n-Pr	n-Pr	CF ₃ CH ₂ -	CF ₃ CH ₂ -	Me	C
	649	Me	Me	CF ₃ CH ₂ -	CF ₃ CH ₂ -	Me	N
15	650	Me	Et	CF ₃ CH ₂ -	CF ₃ CH ₂ -	Me	N
	651	Me	n-Pr	CF ₃ CH ₂ -	CF ₃ CH ₂ -	Me	N
	652	Me	i-Pr	CF ₃ CH ₂ -	CF ₃ CH ₂ -	Me	N
	653	Me	n-Bu	CF ₃ CH ₂ -	CF ₃ CH ₂ -	Me	N
	654	Et	Et	CF ₃ CH ₂ -	CF ₃ CH ₂ -	Me	N
20	655	Et	n-Pr	CF ₃ CH ₂ -	CF ₃ CH ₂ -	Me	N
	656	Et	i-Pr	CF ₃ CH ₂ -	CF ₃ CH ₂ -	Me	N
	657	Et	n-Bu	CF ₃ CH ₂ -	CF ₃ CH ₂ -	Me	N
	658	n-Pr	n-Pr	CF ₃ CH ₂ -	CF ₃ CH ₂ -	Me	N
25	659	H	Me	Me	CF ₃ CH ₂ -	Me	C
	660	H	Et	Me	CF ₃ CH ₂ -	Me	C
	661	H	n-Pr	Me	CF ₃ CH ₂ -	Me	C
30	662	H	i-Pr	Me	CF ₃ CH ₂ -	Me	C
	663	H	n-Bu	Me	CF ₃ CH ₂ -	Me	C
	664	H	Me	Me	CF ₃ CH ₂ -	Me	N
	665	H	Et	Me	CF ₃ CH ₂ -	Me	N
	666	H	n-Pr	Me	CF ₃ CH ₂ -	Me	N
35	667	H	i-Pr	Me	CF ₃ CH ₂ -	Me	N
	668	H	n-Bu	Me	CF ₃ CH ₂ -	Me	N
	669	Me	Me	Me	CF ₃ CH ₂ -	Me	C
40	670	Me	Et	Me	CF ₃ CH ₂ -	Me	C
	671	Me	n-Pr	Me	CF ₃ CH ₂ -	Me	C
	672	Me	i-Pr	Me	CF ₃ CH ₂ -	Me	C
45	673	Me	n-Bu	Me	CF ₃ CH ₂ -	Me	C
	674	Et	Et	Me	CF ₃ CH ₂ -	Me	C
	675	Et	n-Pr	Me	CF ₃ CH ₂ -	Me	C
	676	Et	i-Pr	Me	CF ₃ CH ₂ -	Me	C
	677	Et	n-Bu	Me	CF ₃ CH ₂ -	Me	C
50	678	n-Pr	n-Pr	Me	CF ₃ CH ₂ -	Me	C
	679	Me	Me	Me	CF ₃ CH ₂ -	Me	N

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	680	Me	Et	Me	CF ₃ CH ₂ -	Me	N
	681	Me	n-Pr	Me	CF ₃ CH ₂ -	Me	N
5	682	Me	i-Pr	Me	CF ₃ CH ₂ -	Me	N
	683	Me	n-Bu	Me	CF ₃ CH ₂ -	Me	N
	684	Et	Et	Me	CF ₃ CH ₂ -	Me	N
	685	Et	n-Pr	Me	CF ₃ CH ₂ -	Me	N
10	686	Et	i-Pr	Me	CF ₃ CH ₂ -	Me	N
	687	Et	n-Bu	Me	CF ₃ CH ₂ -	Me	N
	688	n-Pr	n-Pr	Me	CF ₃ CH ₂ -	Me	N
15	689	H	Me	CF ₃ CH ₂ -	H	Me	C
	690	H	Et	CF ₃ CH ₂ -	H	Me	C
	691	H	n-Pr	CF ₃ CH ₂ -	H	Me	C
	692	H	i-Pr	CF ₃ CH ₂ -	H	Me	C
20	693	H	n-Bu	CF ₃ CH ₂ -	H	Me	C
	694	H	Me	CF ₃ CH ₂ -	H	Me	N
	695	H	Et	CF ₃ CH ₂ -	H	Me	N
	696	H	n-Pr	CF ₃ CH ₂ -	H	Me	N
25	697	H	i-Pr	CF ₃ CH ₂ -	H	Me	N
	698	H	n-Bu	CF ₃ CH ₂ -	H	Me	N
	699	Me	Me	CF ₃ CH ₂ -	H	Me	C
30	700	Me	Et	CF ₃ CH ₂ -	H	Me	C
	701	Me	n-Pr	CF ₃ CH ₂ -	H	Me	C
	702	Me	i-Pr	CF ₃ CH ₂ -	H	Me	C
	703	Me	n-Bu	CF ₃ CH ₂ -	H	Me	C
35	704	Et	Et	CF ₃ CH ₂ -	H	Me	C
	705	Et	n-Pr	CF ₃ CH ₂ -	H	Me	C
	706	Et	i-Pr	CF ₃ CH ₂ -	H	Me	C
	707	Et	n-Bu	CF ₃ CH ₂ -	H	Me	C
40	708	n-Pr	n-Pr	CF ₃ CH ₂ -	H	Me	C
	709	Me	Me	CF ₃ CH ₂ -	H	Me	N
	710	Me	Et	CF ₃ CH ₂ -	H	Me	N
45	711	Me	n-Pr	CF ₃ CH ₂ -	H	Me	N
	712	Me	i-Pr	CF ₃ CH ₂ -	H	Me	N
	713	Me	n-Bu	CF ₃ CH ₂ -	H	Me	N
	714	Et	Et	CF ₃ CH ₂ -	H	Me	N
50	715	Et	n-Pr	CF ₃ CH ₂ -	H	Me	N
	716	Et	i-Pr	CF ₃ CH ₂ -	H	Me	N
	717	Et	n-Bu	CF ₃ CH ₂ -	H	Me	N

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	718	n-Pr	n-Pr	CF ₃ CH ₂ -	H	Me	N
	719	H	Me	H	H	Me	C
5	720	H	Et	H	H	Me	C
	721	H	n-Pr	H	H	Me	C
	722	H	i-Pr	H	H	Me	C
	723	H	n-Bu	H	H	Me	C
10	724	H	Me	H	H	Me	N
	725	H	Et	H	H	Me	N
	726	H	n-Pr	H	H	Me	N
	727	H	i-Pr	H	H	Me	N
15	728	H	n-Bu	H	H	Me	N
	729	Me	Me	H	H	Me	C
	730	Me	Et	H	H	Me	C
20	731	Me	n-Pr	H	H	Me	C
	732	Me	i-Pr	H	H	Me	C
	733	Me	n-Bu	H	H	Me	C
	734	Et	Et	H	H	Me	C
25	735	Et	n-Pr	H	H	Me	C
	736	Et	i-Pr	H	H	Me	C
	737	Et	n-Bu	H	H	Me	C
30	738	n-Pr	n-Pr	H	H	Me	C
	739	Me	Me	H	H	Me	N
	740	Me	Et	H	H	Me	N
	741	Me	n-Pr	H	H	Me	N
35	742	Me	i-Pr	H	H	Me	N
	743	Me	n-Bu	H	H	Me	N
	744	Et	Et	H	H	Me	N
	745	Et	n-Pr	H	H	Me	N
40	746	Et	i-Pr	H	H	Me	N
	747	Et	n-Bu	H	H	Me	N
	748	n-Pr	n-Pr	H	H	Me	N
45	749	H	Ph	CF ₃ CH ₂ -	CF ₃ CH ₂ -	Me	C
	750	H	Ph	H	CF ₃ CH ₂ -	Me	C
	751	H	Ph	Me	CF ₃ CH ₂ -	Me	C
	752	H	Ph	H	H	Me	C
50	753	H	Ph	CF ₃ CH ₂ -	CF ₃ CH ₂ -	Me	N
	754	H	Ph	Me	CF ₃ CH ₂ -	Me	N
	755	H	Ph	H	CF ₃ CH ₂ -	Me	N

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	756	H	Ph	H	H	Me	N
	757	Me	Ph	CF ₃ CH ₂ -	CF ₃ CH ₂ -	Me	C
5	758	Me	Ph	Me	CF ₃ CH ₂ -	Me	C
	759	Me	Ph	H	CF ₃ CH ₂ -	Me	C
	760	Me	Ph	H	H	Me	C
10	761	Me	Ph	CF ₃ CH ₂ -	CF ₃ CH ₂ -	Me	N
	762	Me	Ph	Me	CF ₃ CH ₂ -	Me	N
	763	Me	Ph	H	CF ₃ CH ₂ -	Me	N
15	764	Me	Ph	H	H	Me	N

Methods for preparing the compounds of the present invention will be explained below. Among the compounds represented by the general formula (I), the compounds wherein R³ and R⁴ are a C₁-C₆ alkyl group or an ethyl group substituted with one or more halogen atoms can be prepared, for example, according to Reaction Route (1) or (2) set out below.

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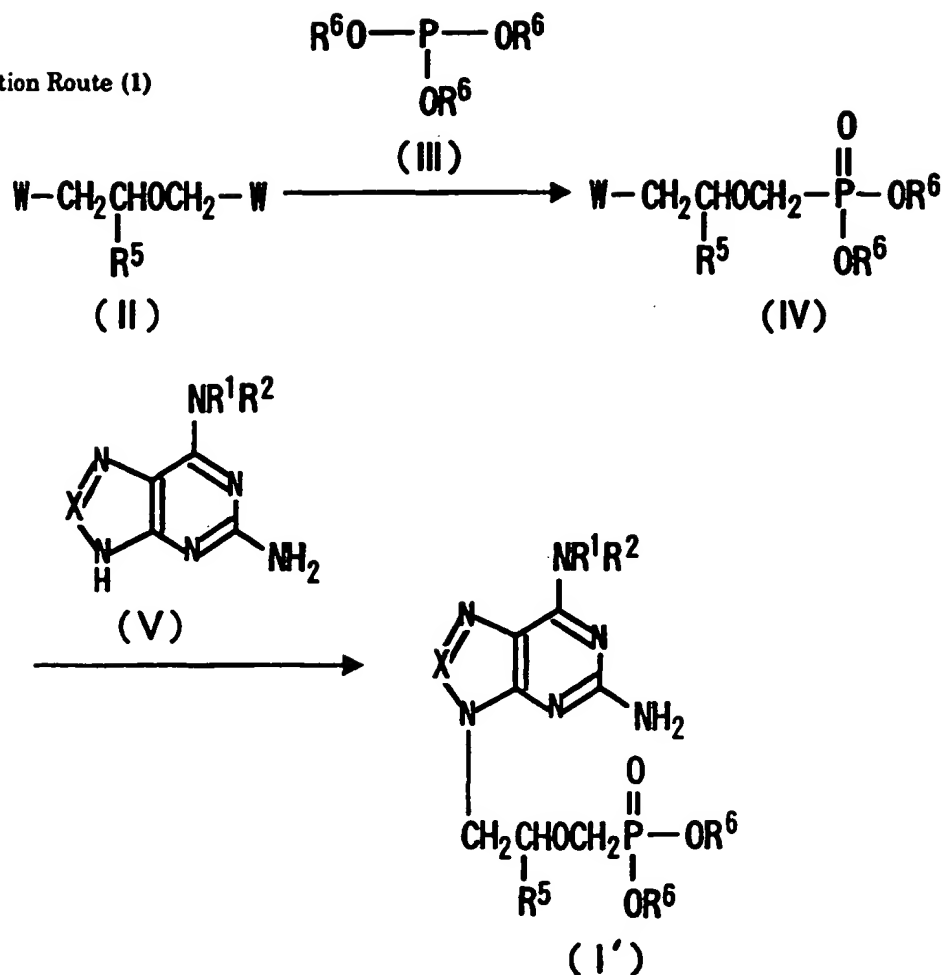
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Reaction Route (1)



In the above scheme, R^1 , R^2 , R^5 , and X have the same meanings as those defined above, and R^6 represents a C_1 - C_4 alkyl group or an ethyl group substituted with one or more halogen atoms. "W" represents a leaving group such as a halogen atom, p-toluenesulfonyloxy group, methanesulfonyloxy group, or trifluoromethanesulfonyloxy group.

A compound of the above general formula (II) and a compound of the above general formula (III) are first allowed to react with each other at a temperature of 10-250°C, preferably 130-180°C for 0.1-20 hours, preferably 3-6 hours. A compound of the above general formula (IV) obtained by the above reaction can be separated and purified according to an ordinary means for separation and purification such as distillation, adsorption or partition chromatography, if necessary. The compound of the above general formula (IV) can be used for the next step after separation and purification as explained above, or alternatively, the product may be subjected to the following reaction without purification.

The compound of the above general formula (IV) is then allowed to react with a compound of the above general formula (V) at a temperature of 10-200°C, preferably 50-150°C for 0.1-100 hours, preferably 5-20 hours in a suitable solvent such as acetonitrile, tetrahydrofuran, dimethyl sulfoxide, dimethylformamide, or methylpyrrolidone in the presence of a base such as sodium carbonate, potassium carbonate, cesium carbonate, sodium hydride, potassium hydride, triethylamine, or diazabicycloundecene to obtain a compound of the above general formula (I').

Sources of the compound of the above general formula (II) as the starting material for Reaction Route (1), the compound of the above general formula (III), and the compound of the above general formula (IV) are not particularly limited. Those commercially available as reagents can be used, or those synthesized by a method known, per se, can also be used. A compound of the general formula (V) can be obtained by heating a compound of the general formula (VI) and a compound of the general formula (VIII), which are mentioned later, at a temperature of 50-100°C in a suitable solvent

such as acetonitrile or dimethyl sulfoxide.

The compound of the above general formula (I') can also be prepared by the method set out below.

Reaction route (2)

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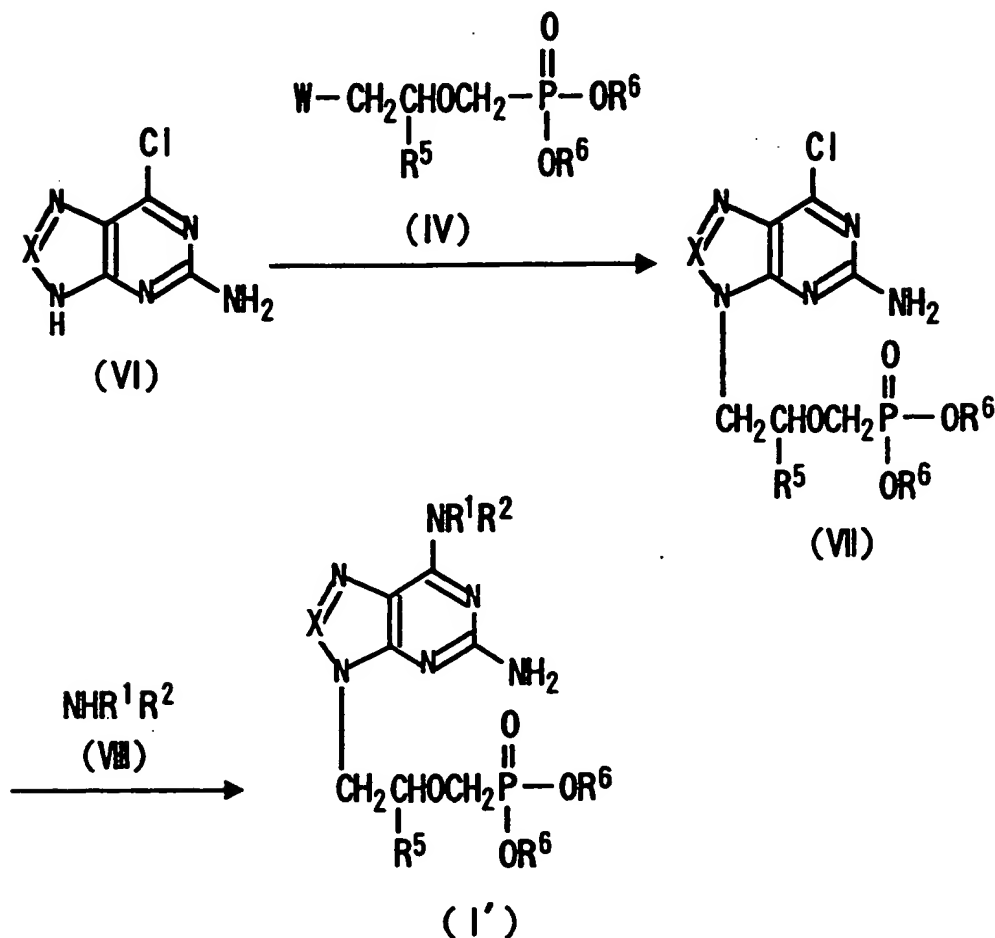
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In the above general formulas R^1 , R^2 , R^5 , R^6 , X, and W have the same meanings as those defined above.

The compound of the above general formula (IV) obtained in Reaction Route (1) and a compound of the above general formula (VI) are allowed to react with each other at a temperature of 10-200°C, preferably 50-150°C for 0.1-100 hours, preferably 5-20 hours in a suitable solvent such as acetonitrile, tetrahydrofuran, dimethyl sulfoxide, dimethylformamide, or methylpyrrolidone in the presence of a base such as sodium carbonate, potassium carbonate, cesium carbonate, sodium hydride, potassium hydride, triethylamine, or diazabicycloundecene to obtain a compound of the above general formula (VII).

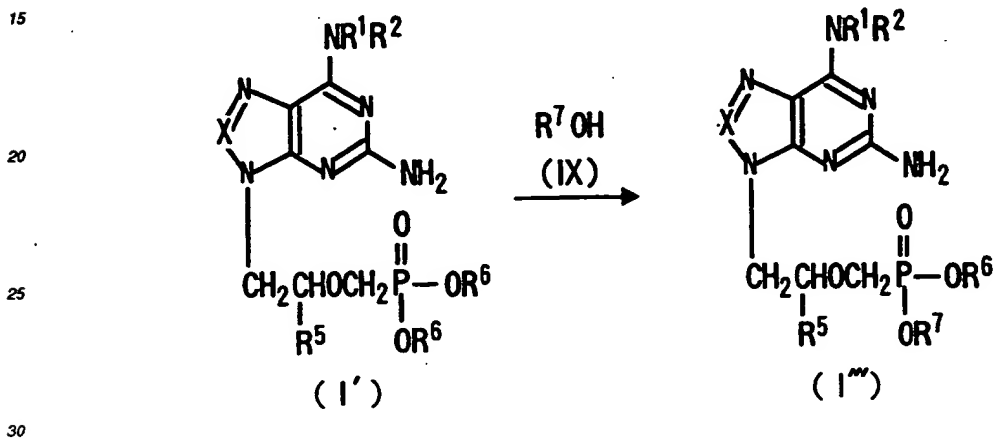
The compound of the above general formula (VII) can be allowed to react with an amine represented by the above general formula (VIII) or hydrochloride thereof at a temperature of 10-200°C, preferably 70-120°C for 0.1-100 hours, preferably 5-12 hours in a suitable solvent such as acetonitrile, tetrahydrofuran, dimethyl sulfoxide, dimethylformamide, or methylpyrrolidone optionally in the presence of a suitable tertiary amine to obtain a compound of the above general formula (I'). The compound of the above general formula (I') corresponds to a compound of the general formula (I) wherein each of R^3 and R^4 is a C_1 - C_6 alkyl group or an ethyl group substituted with one or more halogen atoms.

Sources of the compound of the above general formula (VI) as the starting material for Reaction Route (2) are not particularly limited. Those commercially available as reagents may be used, or those synthesized by a method known per se may also be used.

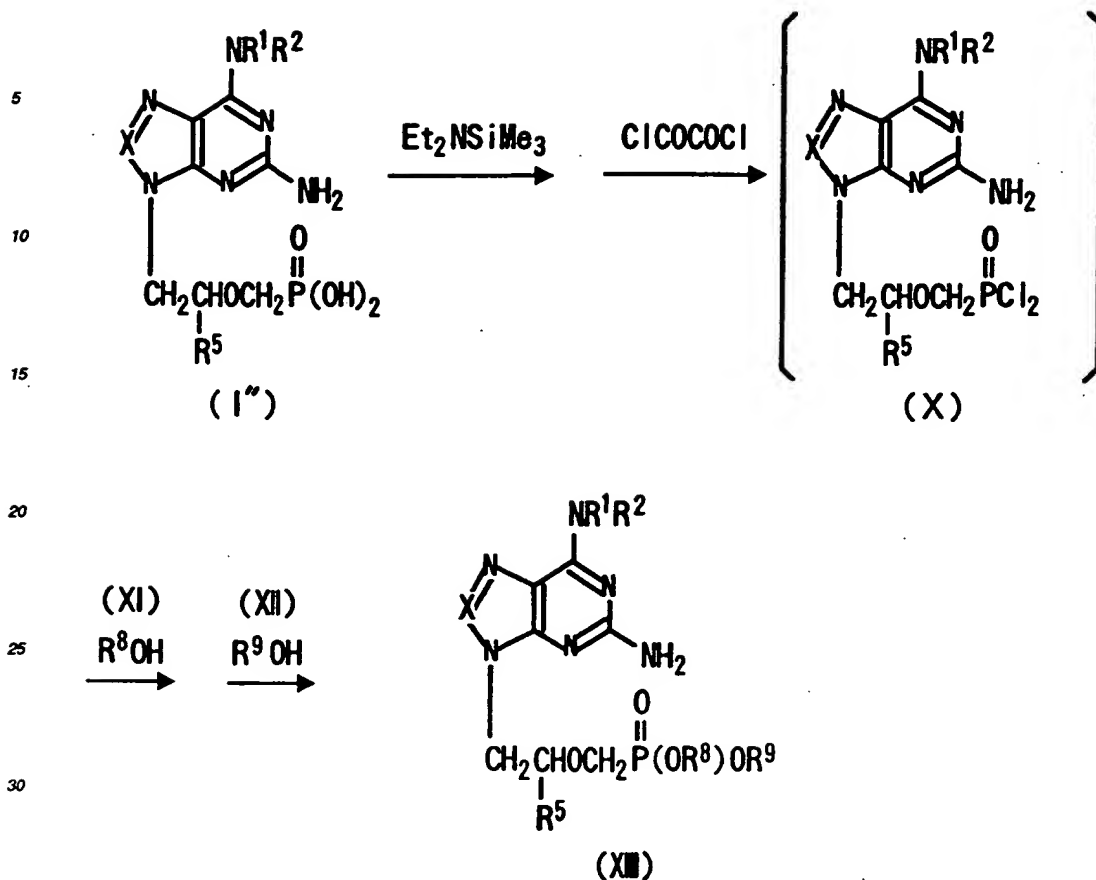
The compound of the general formula (I') is further reacted to obtain a compound of the general formula (I) having a substituent other than R^6 of the compound of the general formula (I').

A compound of the general formula (I) wherein R^3 and R^4 are hydrogen atoms can be obtained by hydrolyzing the compound of the above general formula (I').

5 A compound of the general formula (I) wherein R^3 is hydrogen atom, a C_1 - C_6 alkyl group, an acythioethyl group, or an ethyl group substituted with one or more halogen atoms, and R^4 is a C_1 - C_6 alkyl group or an ethyl group substituted with one or more halogen atoms can be prepared by reacting the compound of the above general formula (I') with a compound of the general formula R^7OH (IX) wherein R^7 represents hydrogen atom, a C_1 - C_4 alkyl group, an acythioethyl group, or an ethyl group substituted with one or more halogen atoms at a temperature of 10-100°C, preferably
 10 20-30°C for 0.1-100 hours, preferably 5-12 hours without solvent or in a suitable solvent, for example, chlorine-containing solvent such as dichloromethane, pyridine, acetonitrile, tetrahydrofuran, dimethyl sulfoxide, dimethylformamide, or methylpyrrolidone, and optionally in the presence of an acid such as p-toluenesulfonic acid, methanesulfonic acid, hydrochloric acid, or phosphoric acid.



35 The compounds of the general formula (I) wherein R^3 and R^4 each independently represent hydrogen atom, a C_1 - C_6 alkyl group, an acythioethyl group, or an ethyl group substituted with one or more halogen atoms can be obtained according to the method set out below.



In the above general formulas, R^1 , R^2 , R^5 , and X have the same meanings as those defined above, and R^8 and R^9 each independently represent a $\text{C}_1\text{-C}_4$ alkyl group, an acylthioethyl group, or an ethyl group substituted with one or more halogen atoms.

A compound of the above general formula (I'') is first reacted with trimethylsilyldiethylamine at a temperature around room temperature for about one hour in a suitable solvent, for example, a chlorine-containing solvent such as dichloromethane, dichloroethane, or chloroform. For this reaction, 2 moles or more of trimethylsilyldiethylamine should be used per 1 mole of the compound of the above general formula (I''). Then, the reaction mixture is concentrated to dryness, and the resulting residue is dissolved in a suitable solvent, for example, a chlorine-containing solvent such as dichloromethane. To this solution, 2 moles or more of oxalyl chloride per 1 mole of the compound of above general formula (I'') is added, and the mixture is allowed to react for about 1 hour under ice cooling and then for about 1 hour at room temperature in the presence of catalytic amount of dimethylformamide.

After evaporating the solvent, the resulting compound of the above general formula (X), usually without further purification, is allowed to react with a compound of the general formula (XI) and/or a compound of the general formula (XII) at a temperature of $10\text{-}100^\circ\text{C}$, preferably $20\text{-}30^\circ\text{C}$ for 0.1-100 hours, preferably 5-12 hours in a suitable solvent such as chlorine-containing solvent such as dichloromethane, pyridine, acetonitrile, tetrahydrofuran, dimethyl sulfoxide, dimethylformamide and methylpyrrolidone. The resulting compound of the general formula (XIII) corresponds to a compound of the general formula (I) wherein each of R^3 and R^4 independently represents hydrogen atom, a $\text{C}_1\text{-C}_4$ alkyl group, an acylthioethyl group, or an ethyl group substituted with one or more halogen atoms.

The compounds of the above general formula (I'') used as the starting material for the above reaction can be obtained by hydrolyzing compounds of general formula (I'), as already explained above, or they can be efficiently obtained by preparing compounds of the above general formula (I') from compounds of the above general formula (IV) wherein R^6 is a $\text{C}_1\text{-C}_4$ alkyl group, and then reacting the resulting product with triethyliodosilane, trimethylbromosilane

or the like.

A compound of general formula (I) wherein each of R^3 and R^4 is an acyloxymethyl group can be obtained by reacting a compound of the general formula (I') with an acyloxymethyl halide represented by the general formula: $R^{10}Y$ (XIV) wherein R^{10} represents an acyloxymethyl group, and Y represents chlorine atom, bromine atom or iodine atom, at a temperature of 0-200°C, preferably 10-100°C for 1-300 hours, preferably 10-200 hours in a suitable solvent such as acetonitrile, tetrahydrofuran, dimethyl sulfoxide, dimethylformamide, or methylpyrrolidone in the presence of a base such as sodium carbonate, potassium carbonate, cesium carbonate, sodium hydride, potassium hydride, triethylamine, pyridine, diazabicycloundecene, or N,N'-dicyclohexyl-4-morpholinecarboxamide.

The compound of the above general formula (I) obtained as described above can be separated from a reaction mixture and purified, if necessary, by applying an ordinary method for separation and purification of a nucleotide compound which can be suitably chosen from, for example, recrystallization, adsorption chromatography, ion exchange chromatography, partition chromatography and the like.

The compounds of the present invention have antiviral activity, as demonstrated in the test examples described later, and are expected to have antitumor activity in the same manner as other ionic phosphonate nucleotide analogues. Target viruses are not particularly limited. Specific examples include RNA viruses such as human immunodeficiency virus, influenza virus and hepatitis C virus, and DNA viruses such as herpes simplex virus I, herpes simplex virus II, cytomegalovirus, herpes zoster varicellous virus, and hepatitis B virus, and a preferred example includes hepatitis B virus.

When the compound of the present invention or a pharmaceutically acceptable salt thereof, or a hydrate or a solvate thereof is used as medicaments, the substance, per se, can be administered, or administered as a pharmaceutical composition prepared in combination with a pharmaceutically acceptable carrier. A sort of the pharmaceutical composition can be decided depending on solubility and chemical properties of the substance, route of administration, dosage regimen and the like. For example, the pharmaceutical composition can be orally administered as a formulation such as, for example, granules, fine granules, powders, tablets, hard syrups, soft capsules, troches, syrups, emulsions, soft gelatin capsules, gels, pastes, suspensions, or liposome formulations, or administered intravenously, intramuscularly, or subcutaneously as an injection. The pharmaceutical composition may also be formulated as a powder for injection, and administered as an injection prepared upon use.

The pharmaceutically acceptable carriers include organic or inorganic solids or liquids for manufacturing pharmaceutical preparations suitable for oral, enteral, parenteral, or topical administration. Examples of the solid carriers for manufacturing solid pharmaceutical compositions include, for example, lactose, sucrose, starch, talc, cellulose, dextrin, kaolin, calcium carbonate, agar, pectin, stearic acid, magnesium stearate, lecithin, sodium chloride and the like. Examples of the liquid carrier for manufacturing liquid pharmaceutical compositions for oral administration include glycerin, peanut oil, polyvinylpyrrolidone, olive oil, ethanol, benzyl alcohol, propylene glycol, physiological saline, water and the like.

The pharmaceutical composition of the present invention may also contain auxiliaries other than the carrier mentioned above, for example, moistening agents, suspending aids, sweeteners, aromatics, colorants, preservatives and the like. Liquid pharmaceutical compositions may be encapsulated in capsules made of absorbable material such as gelatin and administered as capsules. Solvent or suspending medium used for the preparation of pharmaceutical compositions for parenteral administration, i.e., injection or the like, may be, for example, water, propylene glycol, polyethylene glycol, benzyl alcohol, ethyl oleate, lecithin or the like.

The compounds of the present invention, in particular, ester derivatives represented by the above general formula (I') have high oral absorbability, as demonstrated in the test examples described later, and accordingly, pharmaceutical compositions for oral administration are preferred compositions among the pharmaceutical compositions of the present invention. The aforementioned pharmaceutical compositions can be prepared according to ordinary and conventional methods.

Dose may generally be within the range of 1-500 mg/kg, preferably 5-50 mg/kg for an adult based on the compound of the present invention as an active ingredient, when the medicament is administered orally. However, the dose may be appropriately increased or decreased for an administration depending on, for example, age, symptoms, and conditions of a patient, or a use or no use of other drug administered in combination. The aforementioned daily dose may be administered once a day, or the dose may be divided into two or several portions and administered with appropriate intervals. In addition, an administration can be performed intermittently. When used as injection, daily dose may generally be within the range of 0.1-50 mg/kg, preferably 0.1-5 mg/kg for an adult based the compound of the present invention as an active ingredient.

55 Examples

The present invention will be further explained more specifically by referring to the following examples. However, the scope of the present invention is not limited to the following examples.

Example 1: Preparation of 2-amino-9-[2-[bis(2,2,2-trifluoroethyl)phosphonylmethoxy]ethyl]-6-(dimethylamino)purine (Compound No. 11 in Table 1)

2-Chloroethyl chloromethyl ether (87 g, 670 mmol) and tris(2,2,2-trifluoroethyl)phosphite (200 g, 610 mmol) were allowed to react at 160°C for seven hours to obtain 2-[bis(2,2,2-trifluoroethyl)phosphonylmethoxy]ethyl chloride quantitatively.

The 2-[bis(2,2,2-trifluoroethyl)phosphonylmethoxy]ethyl chloride (206 g) was dissolved in methyl ethyl ketone (2000 ml) and the solution was heated under reflux with sodium iodide (270 g) for eight hours. After the reaction was completed, the mixture was cooled to room temperature, and concentrated to dryness. The residue was dissolved in chloroform/hexane and adsorbed on a silica gel in a column, and then eluted with chloroform/hexane to obtain 2-[bis(2,2,2-trifluoroethyl)phosphonylmethoxy]ethyl iodide quantitatively.

2-Amino-6(dimethylamino)purine (7.1 g, 40 mmol) was suspended in dimethyl sulfoxide (300 ml), and reacted with 1,8-diazabicyclo[5.4.0]undec-7-ene (6.6 ml, 44 mmol) at 100°C for one hour. Then, 2-[bis(2,2,2-trifluoroethyl)phosphonylmethoxy]-ethyl iodide (11.5 ml) was added to the reaction mixture, and the mixture was allowed to react at 100°C for two hours. After the reaction was completed, the mixture was cooled to room temperature, and then concentrated to dryness. The residue was dissolved in chloroform and adsorbed on a silica gel in a column, and then eluted with 5%-methanol/chloroform to obtain the title compound (2.35 g, 12%) having the physicochemical properties set out below.

m.p. : 90-92°C (diisopropyl ether)

¹H-NMR (CDCl₃, δ): 3.45 (s, 6H), 3.96-3.85 (m, 4H), 4.20-4.43 (m, 6H), 4.64 (s, 2H), 7.51 (s, 1H)

Example 2: Preparation of 2-amino-9-[2[bis(2,2,2-trifluoroethyl)phosphonylmethoxy]ethyl]-6-(dimethylamino)purine (Compound No. 11 in Table 1)

2-Amino-6-chloropurine (15.0 g, 88 mmol) was suspended in dimethyl-formamide (360 ml), and reacted with 1,8-diazabicyclo[5.4.0]undec-7-ene (13.9 ml, 93 mmol) at 80°C for one hour. Then, 2-[bis(2,2,2-trifluoroethyl)phosphonylmethoxy]-ethyl iodide (23.8 ml) was added to the reaction mixture, and the mixture was allowed to react at 100°C for five hours. After the reaction was completed, the mixture was cooled to room temperature and concentrated to dryness. The residue was dissolved in chloroform and adsorbed on a silica gel in a column, and eluted with 5%-methanol/chloroform to obtain 2-amino-9-[2-[bis(2,2,2-trifluoroethyl)phosphonylmethoxy]ethyl]-6-chloropurine (23.3 g, 56%).

Triethylamine (0.28 ml) and dimethylamine hydrochloride (0.16 g) were added to a solution of the 2-amino-9-[2-[bis(2,2,2-trifluoroethyl)phosphonylmethoxy]ethyl]-6-chloropurine (0.47 g, 1.0 mmol) obtained above in dimethylformamide (4.5 ml), and the mixture was stirred at 100°C for five hours. The reaction mixture was cooled to room temperature and concentrated to dryness. The residue was dissolved in chloroform and adsorbed on a silica gel in a column, and then eluted with 5%-methanol/chloroform to obtain 2-amino-9-[2-[bis(2,2,2-trifluoroethyl)phosphonylmethoxy]ethyl]-6-(dimethylamino)purine (0.33 g, 69%).

Example 3 Preparation of 2-amino-9-[2-[bis(2,2,2-trifluoroethyl)phosphonylmethoxy]ethyl]-6-(diethylamino)purine (Compound No. 16 in Table 1)

The title compound having the physicochemical properties set out below was obtained in the same manner as in Example 2, except that diethylamine was used instead of the dimethylamine hydrochloride.

m.p.: 105-106°C (diisopropyl ether)

¹H-NMR (CDCl₃, δ): 1.24 (t, J = 6.9Hz, 6H), 3.80-4.10 (m, 6H), 4.20-4.48 (m, 6H), 4.54 (s, 2H), 7.51 (s, 1H)

Example 4: Preparation of 2-amino-9-[2-[bis(2,2,2-trifluoroethyl)phosphonylmethoxy]ethyl]-6-(1,1-dipropylamino)purine (Compound No. 20 in Table 1)

The title compound having the physicochemical properties set out below was obtained in the same manner as in Example 2, except that 1,1-dipropylamine was used instead of the dimethylamine hydrochloride.

m.p. : Syrup

¹H-NMR (CDCl₃, δ): 0.93 (t, J = 7.4Hz, 6H), 1.68 (tq, J = 7.6Hz, 4H), 3.60-4.10 (m, 8H), 4.17-4.50 (m, 6H), 4.60 (s, 2H), 7.49 (s, 1H)

Example 5: Preparation of 2-amino-9-[2-[bis(2,2,2-trifluoroethyl)phosphonylmethoxy]ethyl]-6-(methyl-1-propylamino)purine (Compound No. 13 in Table 1)

The title compound having the physicochemical properties set out below was obtained in the same manner as in Example 2, except that methyl-1-propylamine was used instead of the dimethylamine hydrochloride.

m.p. : 88-90°C (diisopropyl ether)

¹H-NMR (CDCl₃, δ): 0.94 (t, J = 7.4 Hz, 6H), 1.55-1.83 (m, 2H), 3.37 (bs, 3H), 3.80-4.10 (m, 6H), 4.20-4.46 (m, 6H), 4.56 (s, 2H), 7.50 (s, 1H)

Example 6: Preparation of 2-amino-8-aza-9-[2[bis(2,2,2-trifluoroethyl)phosphonylmethoxy]ethyl]-6-(dimethylamino)purine (Compound No. 21 in Table 1)

The title compound having the physicochemical properties mentioned below was obtained in the same manner as in Example 1, except that 2-amino-8-aza-6-(dimethylamino)purine was used instead of the 2-amino-6-(dimethylamino)purine.

m.p. : 184-187°C (chloroform)

¹H-NMR (DMSO-d₆, δ): 0.94 (t, J = 7.4 Hz, 6H), 1.55-1.83 (m, 2H), 3.37 (bs, 3H), 3.80-4.10 (m, 6H), 4.20-4.46 (m, 6H), 4.56 (s, 2H), 7.50 (s, 1H)

Example 7: Preparation of 2-amino-9-[2-[bis(2,2,2-trifluoroethyl)phosphonylmethoxy]ethyl]-6-(benzylmethylamino)purine (Compound No. 129 in Table 1)

The title compound having the physicochemical properties set out below was obtained in the same manner as in Example 2, except that benzylmethylamine was used instead of the dimethylamine hydrochloride.

m.p. : 103-105°C (diisopropyl ether)

¹H-NMR (DMSO-d₆, δ): 3.22 (bs, 3H), 3.85 (t, J = 4.9 Hz, 2H), 4.03-4.16 (m, 4H), 4.53-4.80 (m, 4H), 5.22 (bs, 2H), 5.89 (s, 2H), 7.12-7.40 (m, 5H), 7.67 (s, 1H)

Example 8: Preparation of 2-amino-9-[2-[hexyl-(2,2,2-trifluoroethyl)phosphonylmethoxy]ethyl]-6-(dimethylamino)purine

p-Toluenesulfonic acid (10 mg) was added to a solution of 2-amino-9-[2-[bis(2,2,2-trifluoroethyl)phosphonylmethoxy]ethyl]-6-(dimethylamino)purine (0.96 g, 2.0 mmol) in 1-hexanol (5 ml), and the mixture was stirred at 110°C for ten hours. The reaction mixture was cooled to room temperature and concentrated to dryness. The residue was dissolved in chloroform and adsorbed on a silica gel in a column, and eluted with 1%-methanol/chloroform to obtain the title compound (771 mg, 80%).

¹H-NMR (CDCl₃, δ): 0.88 (t, J = 6.6 Hz, 3H), 1.20-1.46 (m, 6H), 1.55-1.72 (m, 2H), 3.45 (s, 6H), 3.80-3.96 (m, involving d at 3.83, J = 8.2 Hz, 4H), 4.00-4.16 (m, 2H), 4.18-4.46 (m, 4H), 4.61 (s, 2H), 7.54 (s, 1H)

Example 9: Preparation of 2-amino-9-[2-bis(2,2,2-trifluoroethyl)phosphonylmethoxy]ethyl]-6-(isopropylmethylamino)purine (Compound No. 14 in Table 1)

The title compound having the physicochemical properties set out below was obtained as oil in the same manner as in Example 2, except that isopropylmethylamine was used instead of the dimethylamine hydrochloride.

¹H-NMR (CDCl₃, δ): 1.24 (d, J = 6.7 Hz, 6H), 3.21 (s, 3H), 3.88-4.02 (m, 4H), 4.17-4.50 (m, 6H), 4.57 (s, 2H), 7.51 (s, 1H)

Example 10: Preparation of 2-amino-9-[2-[bis(2,2,2-trifluoroethyl)phosphonylmethoxy]ethyl]-6-(methylphenylamino)purine (Compound No. 621 in Table 1)

The title compound having the physicochemical properties set out below was obtained in the same manner as in Example 1, except that 2-amino-6-(methyl phenylamino)purine was used instead of the 2-amino-6-(dimethylamino)purine.

m.p. : 147-152°C (ethyl acetate, diisopropyl ether)

¹H-NMR (CDCl₃, δ): 3.78 (s, 3H), 3.86-3.96 (m, involving d at 3.91, J = 7.8Hz, 4H), 4.18-4.48 (m, 6H), 4.61 (s, 2H), 7.24-7.52 (m, 6H)

- 5 Example 11: Preparation of 2-amino-9-[2-[bis(2,2,2-trifluoroethyl)phosphonylmethoxy]ethyl]-6-(phenylamino)purine (Compound No. 613 in Table 1)

The title compound having the physicochemical properties set out below was obtained in the same manner as in Example 1 except that 2-amino-6-(phenylamino)purine was used instead of the 2-amino-6-(dimethylamino)purine.

m.p. : 126°C (isopropanol)

¹H-NMR (CDCl₃, δ): 3.93-3.97 (m, 4H), 4.25-4.44 (m, 6H), 4.82 (s, 2H), 7.05-7.77 (m, 6H)

- 10 Example 12: Preparation of 2-amino-9-[2-[bis(2,2,2-trifluoroethyl)phosphonylmethoxy]propyl]-6-(phenylamino)purine (Compound No. 749 in Table 1)

The title compound having the physicochemical properties set out below was obtained in the same manner as in Example 1, except that 1-chloroisopropyl chloromethyl ether and 2-amino-6-(phenylamino)purine were used instead of the 2-chloroethyl chloromethyl ether and the 2-amino-6-(dimethylamino)purine, respectively.

m.p. : Syrup

¹H-NMR (CDCl₃, δ): 1.26 (d, J = 5.9Hz, 3H), 3.76-3.88 (m, 1H), 3.90-4.10 (m, 3H), 4.16-4.24 (m, 1H), 4.30-4.46 (m, 4H), 4.79 (s, 2H), 7.07 (t, J = 7.4Hz, 1H), 7.35 (t, J = 7.6Hz, 2H), 7.52 (s, 1H), 7.60 (s, 1H), 7.75 (d, J = 7.6Hz, 2H)

- 25 Test Example 1: Activity for inhibiting proliferation of Hepatitis B virus (HBV)

Inhibitory activity of the compounds of the present invention against proliferation of HBV was measured by a known method (K. Ueda, et al., VIROLOGY, 169, 213-216 (1989)).

2 × 10⁴ HB611 cells (recombinant human liver cancer cells producing HBV) were cultured in Dulbecco's ME medium containing 10% fetal bovine serum, streptomycin (100 µg/ml), penicillin (100 IU/ml), and Geneteicin (trade name of an antibiotic sold by Life Technologies, 0.2 mg/ml) at 37°C. The medium was changed with fresh medium on the second day and fifth day of the culture, and then changed with a medium containing a test compound at a final concentration of 10 µM or 1 µM on the 8th, 11th and 14th days of the culture. DNA of the cells were collected on the 17th day of the culture. Amounts of HBV-DNA in the cells were measured by Southern blotting method and inhibitory rates against HBV-DNA synthesis were determined. Concentrations of compounds required for 50% death of HB611 cells were determined. As references, the same test was carried out by using PMEA and its bis(pivaloyloxymethyl ester). The results are shown in Table 2 below. Compound Nos. in Table 2 correspond to those in Table 1.

Table 2

Compound No.	Inhibitory ratio against HBV-DNA synthesis (%)		50% Cytotoxic concentration for HB611 cells (µM)
	10 µM	1 µM	
11	100	92	> 1000
13	100		> 1000
15		86.7	> 1000
16	100		> 1000
21	100		> 1000
621		68	> 1000
PMEA	83		334
PMEA ester ¹	90	63.7	18

¹ PMEA bis(pivaloyloxymethyl ester)

Test Example 2: Inhibitory effect on HBV proliferation in a serum of a rat orally administered with a test compound

A group consisting of three rats was orally administered with a test compound at a dose of 1 g/kg or 0.3 g/kg by a single oral administration. Blood of the rats was collected one hour after the administration and serum samples were prepared.

2×10^4 HB611 cells were cultured in Dulbecco's ME medium containing 10% fetal bovine serum, streptomycin (100 µg/ml), penicillin (100 IU/ml) and Geneteicin (0.2 mg/ml) at 37°C. The medium was changed with fresh medium on the second day and fifth day of the culture, and then changed with a medium containing 5% of the above serum (the serum of the rat orally administered with a test compound) on the 8th, 11th and 14th days of the culture. DNA of the cells were collected on the 17th day of the culture. Amounts of HBV-DNA in the cells were measured by Southern blotting method, and inhibitory ratios against HBV-DNA synthesis in the cells were determined. As a reference, the same test was carried out by using PMEA. The results are shown in Table 3 below. Compound Nos. in Table 3 correspond to those in Table 1.

Table 3

Compound No.	Dose of oral administration (g/kg)	Inhibitory ratio against HBV-DNA synthesis (%)
11	0.3	95.6
13	0.3	100
PMEA	1	35.5

Test Example 3: Micronucleus test using mice

A test compound was administered to mice at a dose of 1,000 or 2,000 mg/kg, and bone marrow smear preparations were prepared at 24, 30, 48, and 72 hours after the administration. For a negative control group (0.5% aqueous solution of tragacanth gum) and a positive control group (2 mg/kg of mitomycin C (MMC) was administered as a single intraperitoneal administration), bone marrow smears were prepared at 24 hours after the administration. The samples were stained by the Giemsa's staining method in an ordinary manner, and then 2,000 polychromatic erythrocytes per animal were examined to determine the number of cells having micronuclei and frequency of appearance of micronuclei (%). As statistic analysis, significant difference test was carried out for polychromatic erythrocytes containing micronuclei between the negative control group and the group administered with a test compound according to the stochastic method of Kasterbaum and Bowman.

For comparison, the same test was carried out by using an unsubstituted 6-amino derivative, i.e., 9-2-[bis(2,2,2-trifluoroethyl)phosphonylmethoxy]ethyl]-2,6-diaminopurine (abbreviated as "DAP"), and PMEA bis(pivaloyloxymethyl ester). The results are shown in Table 4 below. Compound Nos. in Table 4 correspond to those in Table 1.

Table 4

Compound No.	Test result
11	Negative
13	Negative
DAP	Positive
PMEA ester ¹	Positive

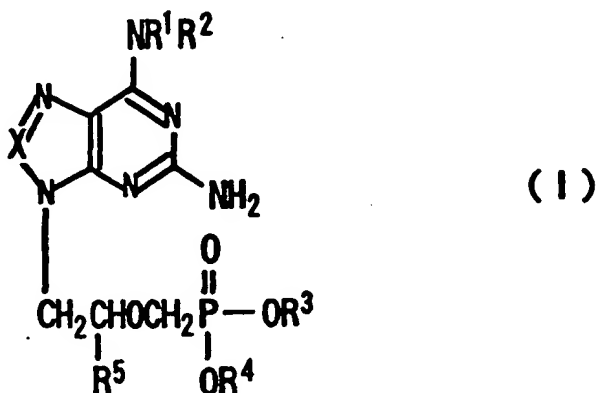
¹ PMEA bis(pivaloyloxymethyl ester)

Industrial Applicability

The phosphonate nucleotide derivatives of the present invention have excellent antiviral activity and high oral absorbability. Therefore, they are expected to be useful as medicaments.

Claims

1. A phosphonate nucleotide derivative represented by the following general formula (I) or a salt thereof, or a hydrate or a solvate thereof:



- wherein R¹ represents hydrogen atom, a C₁-C₆ alkyl group, or a C₇-C₁₀ aralkyl group; R² represents a C₁-C₆ alkyl group, a C₇-C₁₀ aralkyl group, or phenyl group; R³ and R⁴ independently represent hydrogen atom, a C₁-C₆ alkyl group, an acyloxymethyl group, an acythioethyl group, or an ethyl group substituted with one or more halogen atoms; R⁵ represents hydrogen atom, a C₁-C₄ alkyl group, a C₁-C₄ hydroxyalkyl group or a C₁-C₄ alkyl group substituted with one or more halogen atoms; and X represents carbon atom or nitrogen atom.
2. The compound or the salt thereof, or the hydrate or the solvate thereof according to claim 1, wherein R¹ is hydrogen atom or a C₁-C₄ alkyl group; R² is a C₁-C₄ alkyl group, benzyl group, or phenyl group; R³ and R⁴ are independently a C₁-C₆ alkyl group or an ethyl group substituted with one or more halogen atoms; and R⁵ is hydrogen atom or a C₁-C₄ alkyl group.
3. The compound or the salt thereof, or the hydrate or the solvate thereof according to claim 1, wherein R¹ is hydrogen atom or a C₁-C₄ alkyl group; R² is a C₁-C₄ alkyl group or phenyl group; R³ and R⁴ are independently an ethyl group substituted with one or more halogen atoms; and R⁵ is hydrogen atom or a C₁-C₄ alkyl group.
4. The compound or the salt thereof, or the hydrate or the solvate thereof according to any one of claims 1 to 3, wherein R² is phenyl group.
5. The compound or the salt thereof, or the hydrate or the solvate thereof according to claim 1, wherein R¹ is hydrogen atom or a C₁-C₄ alkyl group; R² is phenyl group; R³ and R⁴ are independently an ethyl group substituted with one or more halogen atoms; and R⁵ is hydrogen atom or a C₁-C₄ alkyl group.
6. The compound or the salt thereof, or the hydrate or the solvate thereof according to any one of claims 1 to 3, wherein R⁵ is a C₁-C₄ alkyl group.
7. The compound or the salt thereof, or the hydrate or the solvate thereof according to claim 1, wherein R¹ and R² are independently a C₁-C₄ alkyl group; R³ and R⁴ are independently an ethyl group substituted with one or more halogen atoms; and R⁵ is a C₁-C₄ alkyl group.
8. The compound or the salt thereof, or the hydrate or the solvate thereof according to claim 1, wherein said compound is selected from the group consisting of the following compounds:

2-amino-9-[2-bis(2,2,2-trifluoroethyl)phosphonylmethoxy]ethyl]-6-(phenylamino)purine;
 2-amino-9-[2-bis(2,2,2-trifluoroethyl)phosphonylmethoxy]ethyl]-6-(N-methylphenylamino)purine;
 2-amino-9-[2-bis(2,2,2-trifluoroethyl)phosphonylmethoxy]propyl]-6-(phenylamino)purine;
 2-amino-9-[2-bis(2,2,2-trifluoroethyl)phosphonylmethoxy]propyl]-6-(N-methylphenylamino)purine; and

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2-amino-9-[2-[bis(2,2,2-trifluoroethyl)phosphonylmethoxy]propyl]-6-(dimethylamino)purine.

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9. A medicament comprising the compound or the salt thereof, or the hydrate or the solvate thereof according to any one of claims 1 to 8.
10. A pharmaceutical composition which comprises the compound or the salt thereof, or the hydrate or the solvate thereof according to any one of claims 1 to 8 together with a pharmaceutically acceptable carrier.
- 10 11. An antiviral agent which comprises the compound or the salt thereof, or the hydrate or the solvate thereof according to any one of claims 1 to 8 as an active ingredient.
12. A use of the compound or the salt thereof, or the hydrate or the solvate thereof according to any one of claims 1 to 8 for a manufacture of an antiviral agent comprising the compound or the salt thereof or the hydrate or the solvate thereof as an active ingredient.
- 15 13. A method for therapeutic treatment of a viral infectious disease which comprises the step of administering a therapeutically effective amount of the compound or the salt thereof, or the hydrate or the solvate thereof according to any one of claims 1 to 8 to a patient with the viral disease.
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INTERNATIONAL SEARCH REPORT

International application No.

PCT/JP96/01631

A. CLASSIFICATION OF SUBJECT MATTER

Int. Cl⁶ C07F9/6561, A61K31/675

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

Int. Cl⁶ C07F9/6561, A61K31/675

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAS ONLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO, 94/03467, A2 (Institute of Organic Chemistry and Biochemistry),	1, 2, 6,
Y	February 17, 1994 (17. 02. 94)	9-12
A	& EP, 654037, A1	3, 7-8
		4, 5
Y	JP, 7-70159, A (Mitsubishi Chemical Corp.),	3, 7-8
A	March 14, 1995 (14. 03. 95)	1, 2, 4-6,
	& EP, 632048, A1 & CA, 2126601, A	9-12

☐ Further documents are listed in the continuation of Box C.☐ See patent family annex.

* Special categories of cited documents:

- "A" document defining the general state of the art which is not considered to be of particular relevance

- "E" earlier document but published on or after the international filing date

- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

- "O" document referring to its oral disclosure, use, exhibition or other means

- "T" document published prior to the international filing date but later than the priority date claimed

- "I" later document published after the international filing date or priority date and not in conflict with the application but cited to understate the principle or theory underlying the invention

- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

- "&" document member of the same patent family

Date of the actual completion of the international search

August 16, 1996 (16. 08. 96)

Date of mailing of the international search report

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Name and mailing address of the ISA/

Japanese Patent Office

Facsimile No.

Authorized officer

Telephone No.

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.

PCT/JP96/01631

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 13
because they relate to subject matter not required to be searched by this Authority, namely:
Claim 13 pertains to methods for treatment of the human or animal body by therapy and thus relates to a subject matter which this International Searching Authority is not required, under the provisions of Article 17(2)(a)(i) of the PCT and Rule 39.1(iv) of the Regulations under the PCT, to search.
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐
☐

The additional search fees were accompanied by the applicant's protest.

No protest accompanied the payment of additional search fees.